

CHEMISTRY OF AZIRIDINES

By

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To M. L.

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SPECTRA

Compound	Solvent	
1 Methyl <u>Cis</u> -1-t-Butyl-3-Methyl-2-Aziridinecarboxylate (65)	CCl ₄	 93
2 Methyl <u>Trans</u> -1-t-Butyl-3-Methyl-2-Aziridinecarboxylate (66)	CCl ₄	 93
3 Sodium <u>Cis</u> -1-t-Butyl-3-Methyl-2-Aziridinecarboxylate (67)	D ₂ O	 93
4 Sodium <u>Trans</u> -1-t-Butyl-3-Methyl-2-Aziridinecarboxylate (68)	D ₂ O	 95
5 1-t-Butyl-2-Aziridinecarboxylic Acid Hydrazide (9)	D ₂ O	 95
6 1-Benzyl-2-Aziridinecarboxylic Acid Hydrazide (13)	CDCl ₃	 95
7 1-Phenyl-2-Aziridinecarboxylic Acid Hydrazide (14)	CDCl ₃	 97

SPECTRA (cont'd.)

Compound	Solvent	
8 1-Benzyl-2-Aziridinecarboxylic Acid Hydrazide-Acetone Hydrazone (15)	CDCl ₃	 97
9 1-Phenyl-2-Aziridinecarboxylic Acid Hydrazide-Acetone Hydrazone (16)	CDCl ₃	 97
10 Triphenylmethyl 1-t-Butyl-2- Aziridinecarboxylate (91)	CDCl ₃	 99
11 1-t-Butyl-2-Triphenylmethyl- Aziridine (95)	CDCl ₃	 99
12 1-t-Butyl-3-Chloro-2- Azetidinone (50)	CCl ₄	 99
13 1-t-Butyl-3-Chloro-2- Azetidinone (50)	SO ₂	 101
14 1-t-Butyl-3-Chloro-2- Azetidinone (50)	SbF ₅ ·SO ₂	 101
15 <u>Cis</u> -1-t-Butyl-3-Chloro-4- Methyl-2-Azetidinone (69)	CCl ₄	 101
16 <u>Cis</u> -1-t-Butyl-3-Chloro-4- Methyl-2-Azetidinone (69)	SO ₂	 103
17 <u>Cis</u> -1-t-Butyl-3-Chloro-4- Methyl-2-Azetidinone (69)	SbF ₅ ·SO ₂	 103
18 <u>Trans</u> -1-t-Butyl-3-Chloro-4- Methyl-2-Azetidinone (70)	CCl ₄	 103

SPECTRA

Compound	Solvent	
19 1-t-Butyl-2-Azetidinone (51)	CCl ₄	105
20 1-t-Butyl-2-Azirdinecarboxylic Anhydride (73a)	CCl ₄	105
21 <u>Cis</u> -1-t-Butyl-3-Methyl-2- Aziridinecarboxylic Anhydride (73b)	CCl ₄	105
22 <u>Cis</u> -1-t-Butyl-4-Methyl-1- Azabicyclo [1.1.0.] Butane- 2-One Cation (74)	SO ₂	107
23 <u>Trans</u> -1-t-Butyl-3-Methyl-2- Aziridinecarboxylic Anhydride (73c)	CCl ₄	107
24 <u>Trans</u> -1-t-Butyl-4-Methyl-1- Azabicyclo [1.1.0.] Butane- 2-One Cation (75)	SO ₂	107
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Abstract of Dissertation Presented to the Graduate Council
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CHEMISTRY OF AZIRIDINES

By

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Chairman: James A. Deyrup
Major Department: Chemistry

The unusual reactivity of some 2-aziridinecarboxylic acid derivatives has been investigated. In the course of this study several 1-substituted-2-aziridinecarboxylic acid hydrazides were prepared. The fragmentation of these hydrazides was studied and found to proceed with formation of diimide and ketene intermediates. The mechanistic implications of these results are discussed.

The reaction of sodium 1-t-butyl-2-aziridinecarboxylates with thionyl chloride, oxalyl chloride, and arylsulfonyl chlorides was found to give good yields of 1-t-butyl-3-chloro-2-azetidinones. Stereochemical evidence and product studies suggest the intermediacy of a 1-azabicyclo-[1.1.0.] butane-2-one cation in the ring expansion. This is confirmed by nmr studies of 2-aziridinecarboxylic anhydrides in sulfur dioxide. The synthetic utility of this ring expansion is discussed.

The pyrolysis of triphenylmethyl 1-t-butyl-2-aziridinecarboxylate was investigated as a possible route to a 2-azirine. The pyrolysis did

not generate the 2-azirine, but instead 1-t-butyl-2-triphenylmethyl-aziridine and N-t-butyl-triphenylmethylmethylaniline. The mechanism of this reaction is discussed.

INTRODUCTION

The ultimate goal of the physical organic chemist is the complete understanding of the chemical and physical phenomena associated with all organic matter. The unattainability of this goal forces the chemist to attempt the understanding of simple systems where, by theory and experiment, the frontiers of knowledge can systematically, albeit slowly, be extended. In this manner the concepts of radicals, ions, transition states, molecular orbitals, and the three-dimensional structure of molecules have been born. Reaction mechanisms for many reactions are now understood (or at least thought to be understood), and the effect of additional substituent groups on reaction rates in various systems can quantitatively be predicted with reasonable success.¹

It has been shown that the presence of an unshared pair of electrons situated close to a reaction center in a molecule can enormously affect the rate, direction, and stereochemistry of the reaction. This propinquity effect, neighboring group participation, is quite dependent on the geometry of the substrate.²

Another phenomenon known to dramatically affect the rate and direction of a reaction is ring strain. This is the extra free energy in a cyclic system which can be correlated with the unusual geometry of the molecular orbitals of small ring compounds. The concept of ring strain, first postulated by Adolph von Baeyer in 1885,³ has attracted considerable interest and undergone extensive refinement. The effects of ring strain are most

apparent in ring closure and ring cleavage reactions, and they decrease with increasing ring size as one might expect. Generally heterocyclic rings are not quite as strained as their analogous carbocyclic rings.⁴

TABLE I

Ring Strain Determined From Heats of Combustion^{4b,c}

<u>Compound</u>	<u>Strain(kcal/mol)</u>	<u>Compound</u>	<u>Strain(kcal/mol)</u>
Cyclopropane	27.6	Thietane	19.8
Thiirane	19.6	Cyclopentane	6.5
Oxirane	26.6	Tetrahydrothiophene	3.4
Aziridine	23.0	Tetrahydrofuran	4.6
Cyclobutane	26.0	Pyrrolidine	5.5
Oxetane	26.4	Cyclohexane	0

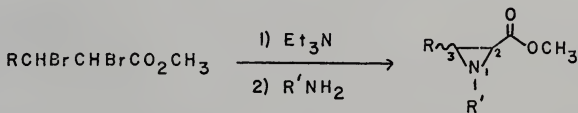
The possible reactivity associated with small strained rings coupled with the possibility of neighboring group participation has stimulated a program of research in this laboratory involving small ring heterocyclic compounds. The research presented here explores the chemistry of some 2-aziridinecarboxylic acid derivatives in an effort to understand the mechanisms of the rearrangements which are found to occur in these systems.

The field of aziridine chemistry is not new. The first aziridine to be formed was the parent compound, ethyleneimine, synthesized by Gabriel (1888)⁵ only three years after Baeyer postulated the Baeyer strain theory. The correct structure was not assigned until 1900.⁶ Since that time a large number of routes to the aziridine system have been discovered, a wide variety of substituent groups has been attached to the ring at all three positions, and the chemistry of many of these compounds has been explored.⁷

The work done to date in this and other laboratories indicates that the electron pair on nitrogen is capable of participating in reactions both on and near the ring. Ring strain also seems to play a major role in the chemistry of this system, and ring cleavage is frequently observed.⁸

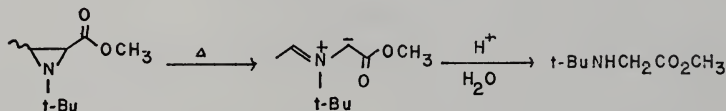
Three classes of 2-aziridinecarboxylic acid derivatives are discussed in this dissertation: 2-aziridinecarboxylic acid hydrazides, 2-aziridinecarboxylic acid salts, and triphenylmethyl 1-t-butyl-2-aziridine-carboxylate. The chemistry of these compounds will be discussed separately in Chapters I, II, and III respectively.

The syntheses of all of these compounds began with the syntheses of the appropriate methyl 2-aziridinecarboxylates. These esters were prepared using procedures patterned after those in the literature by treating the appropriate methyl 2,3-dibromopropionate with triethylamine followed by the appropriate primary amine. These reactions gave rather good yields of the aziridine esters.



In the formation of methyl 1-t-butyl-3-methyl-2-aziridinecarboxylate two isomers were obtained. It was found that the choice of solvent determined which isomer predominated in the product mixture. When the reaction was run in methanol the ratio of cis to trans aziridine was about four to one. When excess t-butylamine was used as the solvent, the ratio of cis to trans aziridine was about three to five. Similar solvent effects have

been observed before in Gabriel-type aziridine syntheses,⁹ and it was considered fortunate that this effect occurred here as it facilitated separation of the isomers. The cis isomer was obtained in a pure state by spinning band distillation of a mixture of the cis and trans isomers. The trans isomer was completely separated from the cis in the same manner, although at first it was not separated from a major impurity believed to be methyl t-butylaminoacetate. The impurity did not interfere with subsequent reactions however. A reasonable mechanism for its formation would involve acid catalyzed hydrolysis of the 1,3-dipole as shown below.*



Later it was found that if the crude aziridine ester was dissolved in benzene and washed with aqueous sodium carbonate prior to the distillation, this difficulty did not arise, and the trans ester was obtained analytically pure.

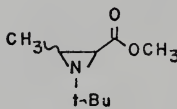
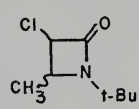
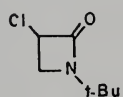
The assignments of stereochemistry to the aziridines and azetidinones to be discussed in Chapter II were made on the basis of coupling constants observed in their nmr spectra. It has previously been shown that the vicinal coupling constants for protons cis to each other on the aziridine

* Refer to Chapter III for a related hydrolysis of an aziridine 1,3-dipole. For an analogous acid catalyzed decomposition, see Reference 10.

ring range between 5 and 8 Hz, but for protons trans to each other the coupling constants drop to between 2 and 5 Hz. Similarly cis coupling constants are larger than trans coupling constants in the azetidinone ring in accord with the Karplus equation.¹² Analysis of the nmr spectra of the aziridines and azetidinones prepared in this work gave the following values for the vicinal coupling constants (TABLE II) The cis stereochemistry was assigned to the isomer having the greater value.

TABLE II

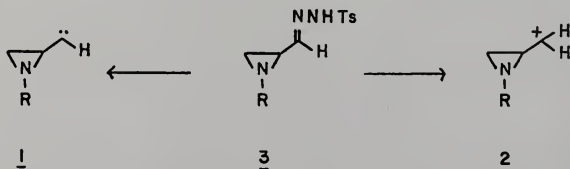
Vicinal Coupling Constants of Aziridine and Azetidinone Ring Protons

<u>Compound</u>	<u>J_{cis}</u> (Hz)	<u>J_{trans}</u> (Hz)
	6.3	2.4
	5.1	1.7
	5.0	2.1

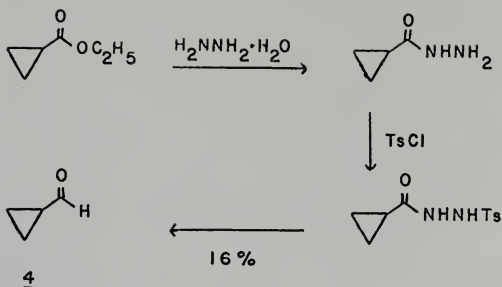
CHAPTER I

REARRANGEMENTS OF 2-AZIRIDINECARBOXYLIC ACID HYDRAZIDES¹⁵

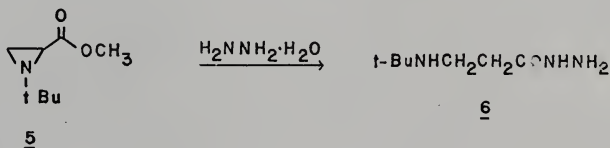
The generation of carbenoid (1)¹⁴ and primary carbonium ion (2) centers on a carbon atom adjacent to the aziridine ring was the original goal of this work. The reactivity of these intermediates should yield considerable insight into the neighboring group effect of the aziridine ring. One synthetic route chosen for generating these species was the thermal decomposition of the tosylhydrazones (3) (Bamford-Stevens Reaction)¹⁵ of appropriate aziridinecarboxaldehydes.¹⁵ The proposed syn-



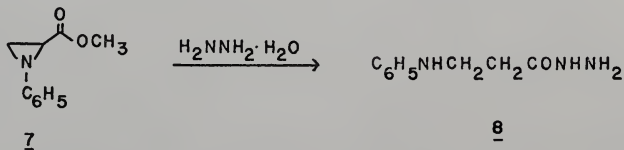
thetic route for formation of the aziridinecarboxaldehydes was patterned after Roberts' synthesis¹⁶ of cyclopropanecarboxaldehyde (4) using the McFayden-Stevens reaction.¹⁷



This route resulted in failure at the first step. When methyl 1-*t*-butyl-2-aziridinecarboxylate (5) was treated with hydrazine hydrate according to normal procedures for the generation of carboxylic acid hydrazides,¹⁸ the only product isolated was 3-*t*-butylaminopropionic acid hydrazide (6) (65%).

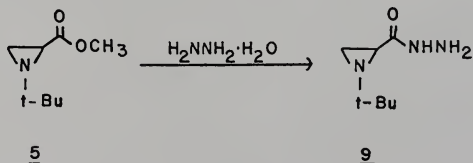


After this work was completed, Professor R. Huisgen pointed out that he had observed a similar reaction with methyl 1-phenyl-2-aziridinecarboxylate (7) and hydrazine hydrate.

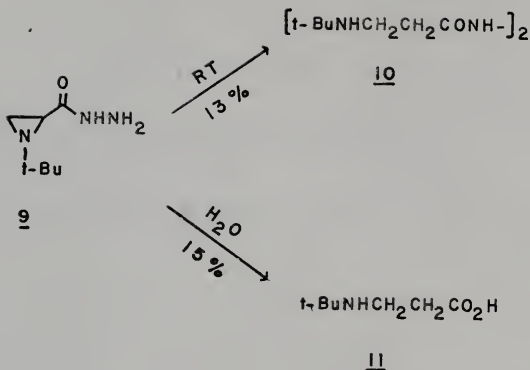


The only comment made by Huisgen concerning the mechanism of the reaction was as follows: "Für diese interessante Hydrogenolyse des Aziridinringes ist uns keine Analogie bekannt."¹⁹ Since the proposed route to the aziridinecarboxaldehyde was no longer promising and since the reductive ring scission was neither expected nor readily explained mechanistically, an investigation of the mechanism of the decomposition of the aziridine-carboxylic acid hydrazides was begun.

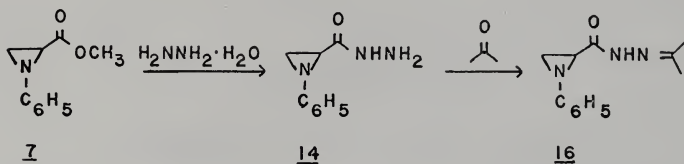
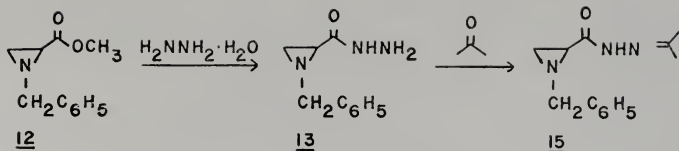
When a slight excess of methyl 1-*t*-butyl-2-aziridinecarboxylate (5) was stirred at room temperature for 9.5 hours with hydrazine hydrate, analysis of the resulting solution (in D₂O) by nmr spectroscopy revealed formation of methanol and a slight change in the pattern and chemical shift of the characteristic three-proton aziridine ring multiplet. Although its instability precluded isolation, the new compound was assigned the structure of 1-*t*-butyl-2-aziridinecarboxylic acid hydrazide (9).



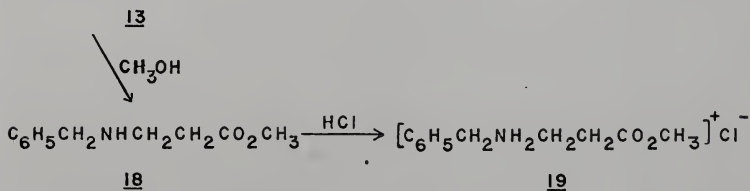
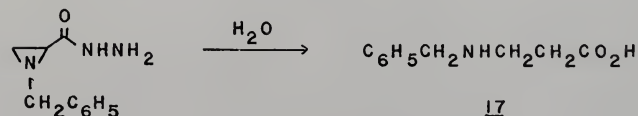
When crude hydrazide 9 was left at room temperature for four days, considerable gas evolution was observed, and a solid identified as 1,2-di-3-*t*-butylaminopropionyl hydrazine (10) precipitated. Refluxing the hydrazide 9 in water produced 3-*t*-butylaminopropionic acid (11) as the only recoverable material.

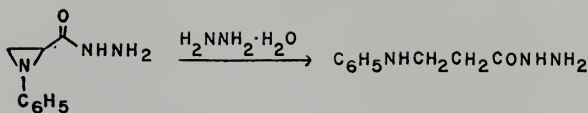


Because 1-t-butyl-2-aziridinecarboxylic acid hydrazide (9) was so unstable, other aziridine hydrazides were sought in the hope that they might be isolable and thus more amenable to study. The reactions of methyl 1-benzyl- and 1-phenyl-2-aziridinecarboxylates (12 and 7) with hydrazine hydrate gave spectrally pure crystalline compounds identified as 1-benzyl- and 1-phenyl-2-aziridinecarboxylic acid hydrazides (13 and 14) respectively. These solids themselves were not very stable but could be kept under nitrogen in the refrigerator for extended periods of time. When dissolved in acetone they formed the corresponding acetone hydrazones (15 and 16). The hydrazones are stable crystalline compounds for which satisfactory elemental analyses were obtained.



Although isolable, the hydrazides 13 and 14 behaved similarly to 1-*t*-butyl-2-aziridinecarboxylic acid hydrazide (9). The benzyl hydrazide (13) gave 3-benzylaminopropionic acid (17) when refluxed in water and methyl 3-benzylaminopropionate (18), identified as its hydrochloride (19), when refluxed in methanol. The phenyl hydrazide (14), when refluxed with excess hydrazine hydrate in ethanol, ring opened to form 3-anilinopropionic acid hydrazide (8).



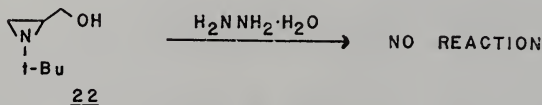
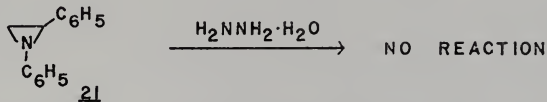
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Numerous mechanisms can be formulated which are capable of explaining the observed products. The first to be considered is a direct reduction of the aziridine ring by either hydrazine or perhaps diimide^{*} derived from hydrazine. The intermediacy of diimide has been well established in reductions involving hydrazine. The reduction of symmetrical double bonds proceeds smoothly and stereospecifically to give cis addition of hydrogen. The reaction is thought to be concerted, involving a six-membered cyclic transition state (20).²⁰

20

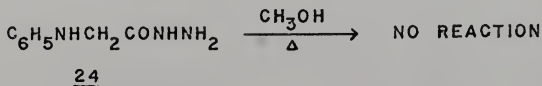
* Prior oxidation of hydrazine, possibly by air, would be necessary.

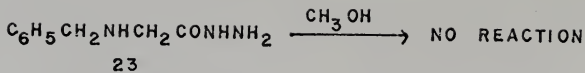
In an analogous manner concerted reduction of the aziridine ring was also conceivable. Driving forces for the reduction would be relief of ring strain and formation of nitrogen. However, 1,2-diphenylaziridine (21) and 1-*t*-butyl-2-aziridinecarbinol (22) were stable to hydrazine hydrate under the reaction conditions.



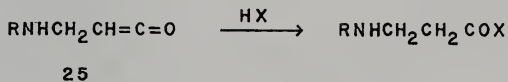
This result combined with the observation that aziridine hydrazides were isolated and then allowed to ring open rules out the possibility of direct ring scission by hydrazine.

The role the aziridine ring plays in the reaction also deserves investigation. The observations that benzylamino- and anilinoacetic acid hydrazides (23 and 24) are stable to the reaction conditions implies that the reactivity observed is not to be associated with α -amino acid hydrazides but indeed is in some way associated with the aziridine ring. It is pertinent too that cyclopropanecarboxylic acid hydrazide, the carbocyclic analog, is a stable compound, apparently not enjoying this reactivity.¹⁶

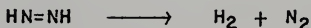
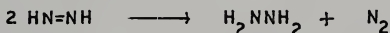




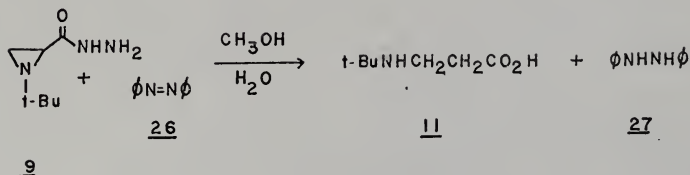
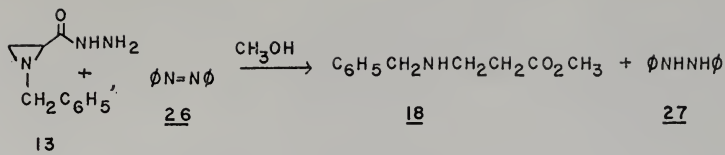
Careful inspection of the above data suggested that the aziridine hydrazide rearrangement might involve formation of diimide and an amino-ketene intermediate. The aminoketene intermediate (25) nicely accounts for all of the amino acid derivatives observed as products of the rearrangement.²¹



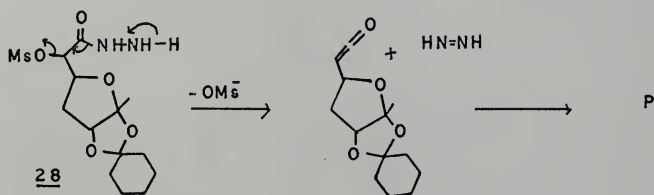
Formation of diimide accounts for the copious gas evolution observed. Diimide is an extremely unstable compound although it does have a finite lifetime as is evidenced by its isolation at low temperature followed by decomposition on warming.²² Two pathways are available for thermal decomposition, both of which yield gaseous products. Reduction of a second mole of diimide to form hydrazine and nitrogen seems to be favored over spontaneous decomposition into hydrogen and nitrogen.²³



Confirmatory evidence for the presence of diimide was in fact obtained by observing concomitant reduction of azobenzene (26) to hydrazobenzene (27)²⁴ during the conversion of 1-benzyl-2-aziridinecarboxylic acid hydrazide (13) to methyl 3-benzylaminopropionate (18) as well as in the conversion of 1-butyl-2-aziridinecarboxylic acid hydrazide (9) to 3-t-butylaminopropionic acid (11).



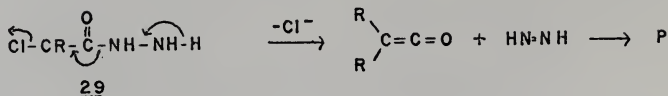
The fragmentation of α -substituted carboxylic acid hydrazides to ketenes and diimide has been observed before. For example, Paulson and Stoye²⁵ have studied the fragmentation of α -mesyl hydrazide 28 and observed the formation of a ketene at the relatively* low temperature of 50°.



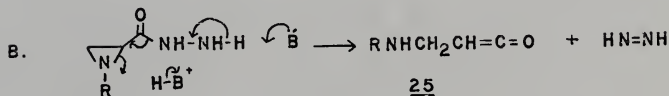
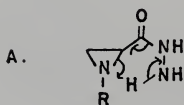
Buyle has studied the base catalyzed fragmentation of mono-, di-, and tri-chloroacetic acid hydrazide hydrochlorides (29).²⁷ These two apparently

* The temperatures generally required to pyrolyze alkyl and aryl carboxylic acid hydrazides are on the order of 150-175°.²⁶

undergo a Grob type fragmentation generating ketenes and diimide.



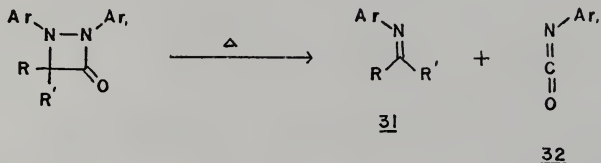
There are number of detailed paths* by which a 2-aziridinecarboxylic acid hydrazide could fragment to form diimide and an aminoketene (25).



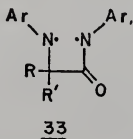
* These formulations are not intended to imply any necessarily concerted timing in the events leading from the hydrazides to the products.

Mechanism C can tentatively be ruled out in view of the known course of intramolecular aziridine and epoxide ring openings.²⁸ Thus one would expect attack to occur at the 3-position and not at the 2-position.

Also, based on what is known about the chemistry of 1,2-diazetidines, the suggested intermediate (30) should be stable under the reaction conditions. The 2,3-diazetidines synthesized to date are generally substituted at the 1- and 2-positions. They do decompose at elevated temperatures, but to form isocyanates (32) and Schiff bases (31).²⁹



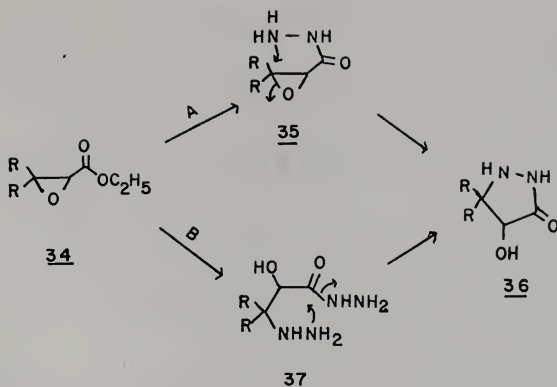
The observation that the cleavage is facilitated by electron withdrawing groups at the 1- and 2-positions has been interpreted as evidence for a diradical intermediate (33) formed by rupture of the weak N-N bond.³⁰



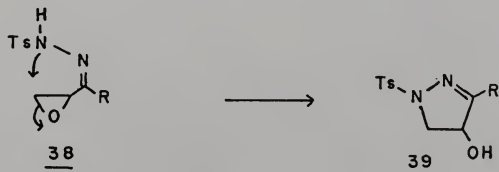
Since the postulated intermediate diazetidinones (30) do not have radical stabilizing groups at either the 1- or 2-position, it is expected that this type of cleavage would not readily occur. Cleavage to form diazo and ketene intermediates has not been observed, and it seems reasonable that this would be an even higher energy process.

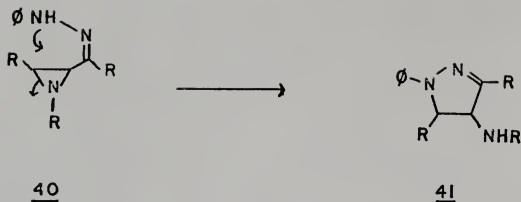
The data available are not sufficient to distinguish between the first two mechanisms (A and B), both of which are Grob type fragmentations.³¹ Although in non-hydrogen bonding solvents the hydrazides might be expected to exist in an intramolecularly hydrogen bonded conformation such that fragmentation would readily proceed according to mechanism A, the solvents used here (i.e., water, methanol, ethanol) might seriously affect the conformation assumed by the hydrazide. Because of this it is difficult to differentiate between the first two mechanisms. It would be possible to gain some insight via a kinetic investigation, but the hydrazides were never purified enough to make such a kinetic investigation feasible.

A perhaps more interesting problem arises when this reaction is contrasted with the rearrangements of epoxy hydrazides. Martynov and Belov^{28a} allowed epoxy esters (34) to react with hydrazine and were unable to isolate the epoxy hydrazides (35). Instead, they obtained hydroxy pyrazolidones (36). The data which they presented was not considered sufficient proof of structure for the pyrazolidones however. Following their procedure, ethyl β , β -tetramethyleneglycidate was heated with hydrazine hydrate. Nmr and mass spectroscopy verify the pyrazolidone structure of the crystalline product. The mechanism of this rearrangement presumably involves intramolecular nucleophilic attack at the 3-position of the epoxide ring (route A). Initial attack of hydrazine at the 3-position to open to a hydrazine intermediate (37) followed by ring (route B) closure to the pyrazolidone has also been suggested.³² The question remains, why do epoxy and aziridinecarboxylic acid hydrazides react so differently?



The aziridinecarboxylic acid hydrazone decomposition also contrasts remarkably with rearrangements of aziridine and epoxy hydrazones. Padwa^{28b} has shown that the tosylhydrazones of epoxy ketones (38) rearrange to form 4-hydroxy pyrazolines (39), and Cromwell *et al.*,^{28c} have shown that phenyl hydrazones of aziridine ketones (40) rearrange to form 4-amino pyrazolines (41). These rearrangements have been explained by postulating intramolecular nucleophilic attack at the 3-position of the heterocycle.





Again, why does the aziridinecarboxylic acid hydrazide fail to rearrange by intramolecular attack at the 3-position to form an aminopyrazolidone? The nature of the heteroatom (O,N) probably does not play the major role in directing the course of the reactions since both epoxy and aziridine hydrazones undergo analogous rearrangements. The answer probably lies in steric and conformational effects which could be greatly affected by substituent groups on the ring and to a lesser extent by the heteroatom and groups on the heteroatom. There may be a fantastic Franconi effect facilitating fragmentation relative to intramolecular rearrangement of the aziridinecarboxylic acid hydrazides.³¹

In any case, it can be concluded here that 2-aziridinecarboxylic acid hydrazides do fragment to form aminoketenes and diimide. One important driving force is relief of ring strain. The reaction appears to be general for aziridines with various substituents on nitrogen (aryl and alkyl). The reaction may or may not find synthetic utility, but mechanistically it does deserve further investigation.

Another problem deserving further attention is the original goal of this work - generation of carbenoid and primary carbonium ion centers adjacent to the aziridine ring.

CHAPTER II

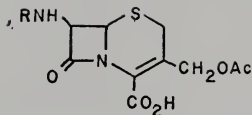
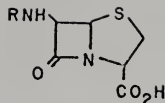
FORMATION AND REACTIVITY OF 1-t-BUTYL-3-CHLORO-2-AZETIDINONES

Formation of 3-Chloro-2-Azetidinones

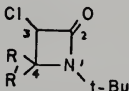
The 2-azetidinone ring was first successfully synthesized in 1907 when H. Staudinger observed that cyclization of diphenylketene (42) and benzaldehyde anil (43) yielded 1,3,3,4-tetraphenyl-2-azetidinone (44).³³



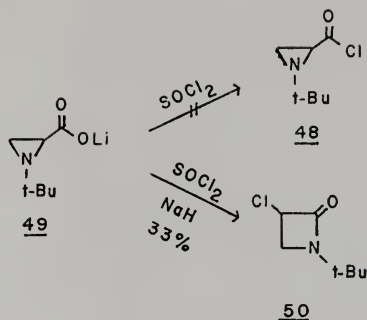
Since that time 2-azetidinones (β -lactams) have attracted considerable interest as a reactive strained heterocyclic ring system and as a key part of biologically active cephalosporin (45) and penicillin (46) structures. Because of the biological activity of these systems, a variety of routes have been developed to generate the azetidinone ring, and some aspects of the chemistry of azetidinones have been investigated.³⁴ Most of the research in this field has been carried out since World War II and includes the total synthesis of penicillins.³⁵

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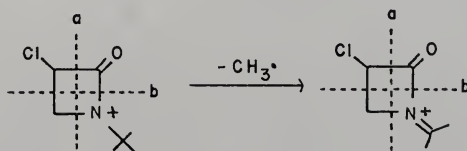
This chapter will deal with the discovery that certain aziridine derivatives undergo ring expansion to 3-halo-2-azetidiones (47). Some of the reactions characteristic of this heterocyclic ring will also be discussed.

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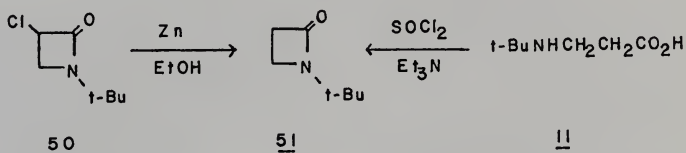
This work began when an attempt to synthesize a 2-aziridinecarbonyl chloride (48) resulted in a new path³⁶ to the 3-halo-2-azetidione system. When lithium 1-*t*-butyl-2-aziridinecarboxylate (49) was treated with thionyl chloride in the presence of excess sodium hydride, a 33% yield of 1-*t*-butyl-3-chloro-2-azetidione (50) was obtained.



The structure of the azetidinone (50) was assigned on the basis of the nmr spectrum, a carbonyl absorption in the ir at 1760 cm^{-1} (characteristic of the azetidinone ring),³⁷ and a satisfactory elemental analysis. The mass spectrum showed parent ions at m/q 161 and 163 in the proper ratio for the chlorine isotopes as well as cleavage of the ring in both directions (a and b) as expected from published mass spectral studies of 2-azetidinones.³⁸

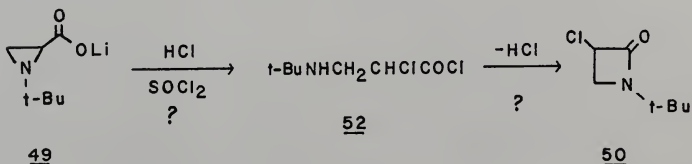


Further proof of structure was obtained by reduction of 50 to 1-t-butyl-2-azetidinone (51) with zinc dust in refluxing ethanol, a procedure patterned after that of Knunyants and Gambaryan.^{36b} The same azetidinone was then synthesized in low yield from 3-t-butylaminopropionic acid (11) and thionyl chloride.³⁹

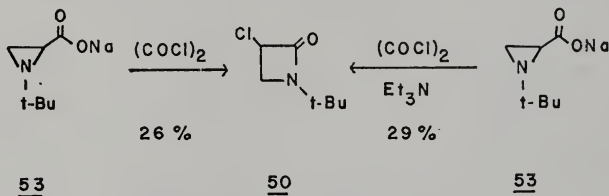


The ring expansion was considered to be of both mechanistic and synthetic interest, and thus further investigation of the reaction was initiated.

Several mechanisms could reasonably account for the ring expansion. The first route to be considered was acid catalyzed ring opening of the aziridine to give an α -chloro- β -amino acid. This species might then react with thionyl chloride to form the amino acid chloride (52) which could, in turn, ring close to the 2-azetidinone (50).³⁹

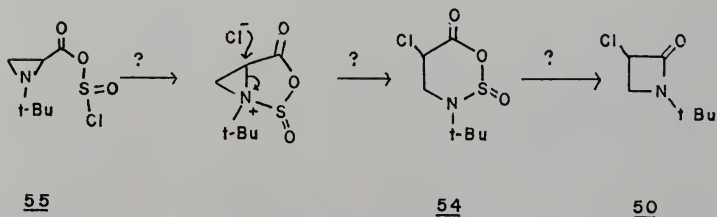


Several observations make this route unlikely. The reaction with thionyl chloride was not inhibited by excess sodium hydride. The ring expansion also proceeded when sodium 1-t-butyl-2-aziridinecarboxylate (53) was treated with oxalyl chloride, and the yield was not diminished when this reaction was rerun in the presence of triethylamine.

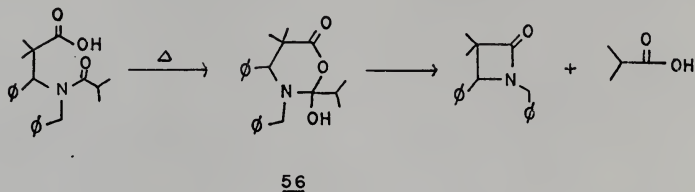


It is unlikely that acidic ring opening of the aziridine would occur under either of the above basic conditions.⁴⁰

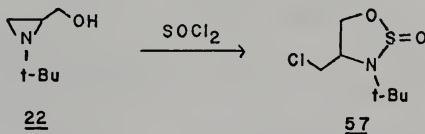
The second route to be considered involves transient formation of a six-membered heterocyclic intermediate (54) via mixed anhydride 55. Subsequent loss of sulfur dioxide from 54 might generate the 2-azetidinone (50).



Precedent for the ring contraction can be found in the pyrolysis of β -acylamino acids where formation of a six-membered cyclic intermediate (56) is postulated.⁴¹



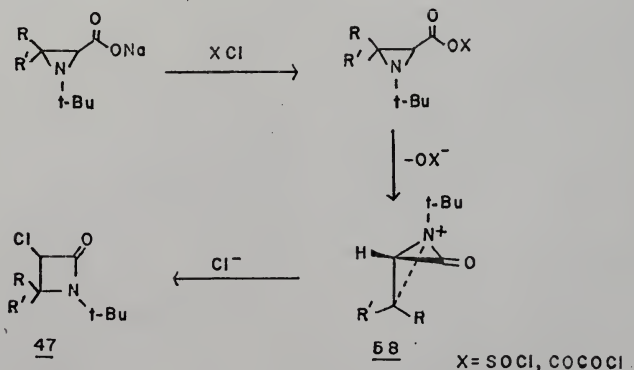
Attack by the annular nitrogen at sulfur finds some analogy in the formation and isolation of oxathiazolidine 57 in the reaction of aziridinol 22 with thionyl chloride.⁴⁰



This mechanism, however, appears unlikely for several reasons. In the first place, the similar yields and products obtained with oxalyl chloride are suggestive of a common intermediate in both reactions. Secondly, the best available analogies (e.g., 57)⁴⁰ imply that 54 (as well as the unlikely seven-membered ring analog required by this mechanism for oxalyl chloride) would be stable under the mild conditions of the reaction. Finally, the ring expansion of 2-aziridinecarboxylic acid anhy-

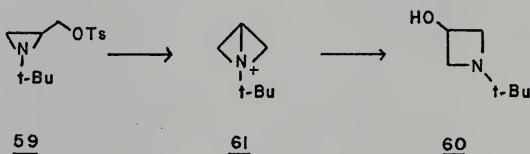
drides to be discussed below is also incompatible with a mechanism involving cyclic intermediates.

A mechanism which is capable of explaining the results involves interaction of the unshared pair of electrons on the annular nitrogen and the carbonyl carbon resulting in formation of a 1-azabicyclo [1.1.0]-butane-2-one cation (58). An examination of models suggests that the unshared pair of electrons on nitrogen is oriented favorably for overlap at the carbonyl carbon. Thus the bond deformations and additional strain required for participation does not appear to be severe.* The resulting cation 58 may then be captured at the 3-position by chloride to generate the chlorazetidione according to the following scheme:

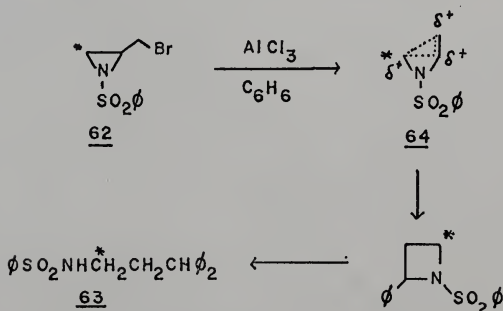


* Analogous participation by nitrogen at a carbonyl carbon has been used to rationalize enhanced rates of hydrolysis of γ -amino esters.⁴²

Although this ion has no exact literature precedent, a number of 1-azabicyclo [1.1.0.] butane cations have been postulated as reaction intermediates in ring expansions of aziridines to azetidines. In this laboratory solvolysis of aziridinecarbinyl tosylates (59) were found to give azetidinols (60) under certain conditions. This ring expansion is thought to involve a 1-azabicyclo [1.1.0.] butonium ion (61) as an intermediate.⁴³



W. Gensler and coworkers have shown that the reaction of labeled aziridinecarbinyl bromide 62 with aluminum chloride in benzene to form ring opened amine 63 proceeds through an azetidine intermediate. It was suggested that this might result from an azabicyclobutonium ion represented as 64.⁴⁴



The stability of the azabicyclobutane ring has recently been demonstrated by the synthesis and isolation of 3-phenyl-1-azabicyclo [1.1.0.]butane by Hortmann and coworkers.⁴⁵ The introduction of a carbonyl group, as in 58, would be expected to cause an increase in strain. For example, Wiberg has shown that the introduction of a trigonal carbon in a three-membered ring results in approximately 13 kcal/mol additional strain energy (Table III).⁴⁶

TABLE III

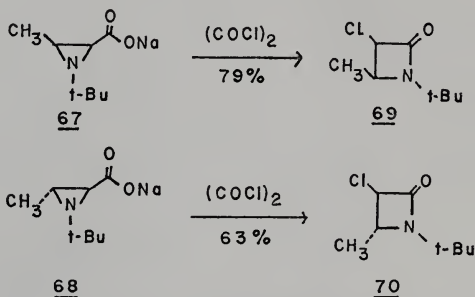
Ring Strain in Three-Membered Rings

<u>Compound</u>	<u>Strain Energy kcal/mol</u>
Cyclopropane	27.5
Methylenecyclopropane	41.0
Cyclopropene	53.1

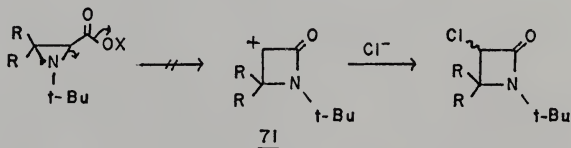
This additional strain would increase the energy of the intermediate (58), but would not preclude its formation.

If the 1-azabicyclo [1.1.0.] butane-2-one cation (58) were actually involved in the ring expansion, the reaction should be stereospecific. Attack by chloride at the 3-position should occur at the back side of the C-N bond, i.e., endo⁴⁷ to the puckered ring. In order to test this hypothesis, the sodium salts of both cis- and trans-1-t-butyl-3-methyl-2-aziridinecarboxylic acid (67 and 68) were prepared by stereospecific base catalyzed hydrolysis of the corresponding aziridine esters (65 and 66). These salts were treated with oxalyl chloride in benzene, and the resulting ring expansions were indeed stereospecific. The cis aziridine

(67) gave the cis azetidinone (69),* and the trans aziridine (68) gave the trans azetidinone (70) as predicted. The reactions went in high yield and with no detectable (nmr) isomeric contamination.

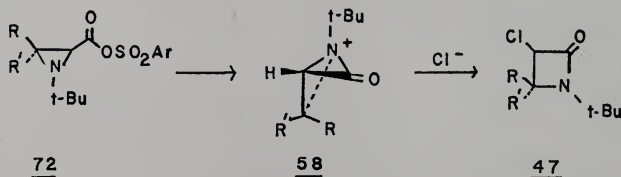


The stereospecificity of the ring expansion strongly supports the intermediacy of the 1-azabicyclo [1.1.0.] butane-2-one cation (58) and unequivocally rules out the possibility of an α -carbonyl cation (71).



* Elemental analysis of 69 did not check. However all spectral properties were in accord with the proposed structure. The mass spectrum was essentially identical to that of 70.

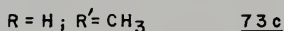
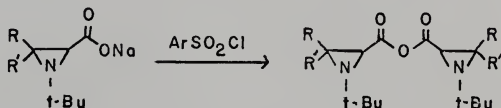
It was hoped further evidence for the ionic mechanism could be obtained from reaction of the sodium aziridinecarboxylates (53, 67, and 68) with nosyl and tosyl chloride to form mixed anhydrides (72). Mixed tosyl carboxylic acid anhydrides have been isolated,⁴⁸ and there is precedent for their existence as reactive intermediates in some rearrangements.⁴⁹ Conceivably, participation at the carbonyl carbon by nitrogen might induce ionization of the mixed anhydride and thus lead again to the postulated bicyclic cations (58). The resulting cations should be captured in the 3-position by nucleophiles to generate the 2-azetidiones as before.



Reaction of equivalent amounts of the sodium 2-aziridinecarboxylates (53, 67, and 68) with nosyl or tosyl chloride did not yield the mixed anhydrides. Instead, mixtures of the sulfonyl chloride and the symmetrical aziridine anhydrides (73) were recovered.* The symmetrical anhydride (73b) was formed free of nosyl chloride when two equivalents of the sodium salt were allowed to react with one equivalent of nosyl chloride.

* Nosyl chloride was removed by fractional crystallization, leaving the anhydride (73b) behind.

The structure of the anhydride is based on the nmr spectrum (CCl_4 -characteristic of the aziridine ring), and absorptions in the ir at 1820, and 1760 cm^{-1} (characteristic of anhydrides).⁵⁰ Chemical evidence for the anhydride structure was obtained by recovering both sodium 2-aziridine carboxylate (67) and methyl 2-aziridinecarboxylate (65, 35%) from the reaction of 73b with sodium methoxide in methanol.

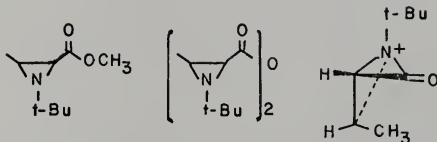


Strong evidence for the bicyclic cation (58) was obtained from the nmr spectra of the aziridine anhydrides (73) in sulfur dioxide.⁵¹ A cold concentrated sulfur dioxide solution of the *cis* anhydride (73b) gave an nmr spectrum in accord with the anhydride structure. A more dilute solution, after standing at room temperature for a short time, gave an nmr spectrum with two sets of signals of similar pattern, one set at a chemical shift characteristic of the anhydride, and one set displaced downfield by an amount $\Delta\delta$ ppm (Table IV). Both the unionized aziridine anhydride and the aziridinecarboxylate anion are assigned as the species responsible for the upfield set of signals, and the bicyclic cation structure (74) is assigned to the species responsible for the downfield set of signals (Table IV).

TABLE IV

Chemical Shifts (δ) in Sulfur Dioxide Relative to External Tetramethylsilane in Carbon Tetrachloride

Substrate



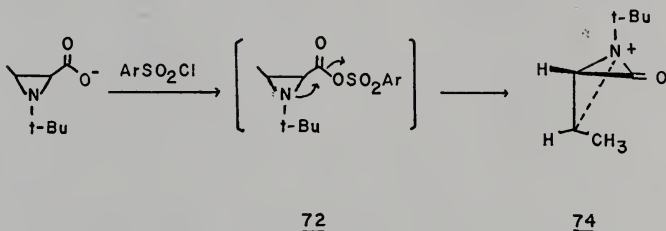
R	<u>65</u>	<u>73b</u>	<u>74</u>	$\Delta\delta$ ppm
t-Bu	0.40	0.39	0.76^a 0.78^b	0.38^c
CHCH	1.72	1.78	2.76 2.80	1.00
CH ₃	0.58	0.62	0.93 0.95	0.32

^aCounterion = tosylate.

^bCounterion = nosylate.

^cDifference in chemical shifts of anhydride 73b and average of ions 74^{a,b}.

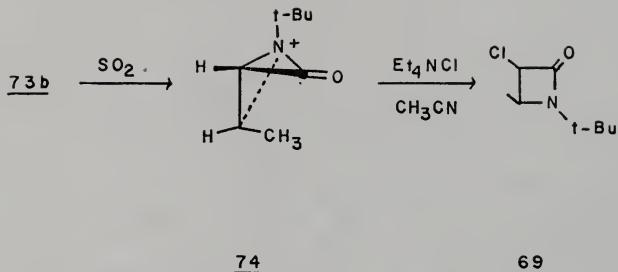
Addition of nosyl chloride or tosyl chloride to these solutions resulted in the disappearance of the upfield set of signals and enhancement of the downfield set of signals, presumably by ionization of the newly formed mixed anhydride (72).



The value of $\Delta\delta$ ppm (1.00) observed for the ring hydrogens of 74 is quite similar to that observed by Olah (1.20) for 1-t-butylaziridinium ion in both antimony pentafluoride-sulfur dioxide and acidic sulfur dioxide. The chemical shift of the t-butyl group (δ 0.78) is not similar to that observed by Olah and Szilagyi (δ 1.26).⁵² This discrepancy can be rationalized by differences in counterion, solvation and concentration effects,* and anisotropic effects due to the bicyclic ring.

Further chemical evidence for the bicyclic cation (74) was obtained when the sulfur dioxide solutions were quenched with tetraethyl ammonium chloride in acetonitrile to stereospecifically give 69.

* Olah and Szilagyi observed differences in the chemical shifts of the same aziridinium ion of as much as 0.2 ppm with changes in $[\text{H}^+]$ and gegenion.⁵²

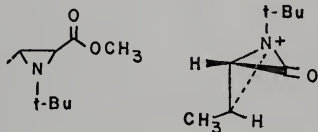


Similar results were obtained with the trans anhydride (73c). A sulfur dioxide solution of the anhydride (73c) in the presence of nosyl chloride initially showed two sets of signals attributable to the unionized anhydride and the carboxylate anion (upfield set of signals) and the bicyclic cation (75) (downfield set of signals), but decomposition was so rapid that the spectrum obtained was not at all satisfactory. At -20° a clean spectrum of the bicyclic cation was obtained. Again, values of δ and $\Delta\delta$ ppm for the tertiary butyl group and the ring hydrogens were in accord with expectations (Table V). On warming, these signals disappeared with concomitant formation of a new set of signals attributable to trans-1-*t*-butyl-3-chloro-4-methyl-2-azetidinone (70).

TABLE V

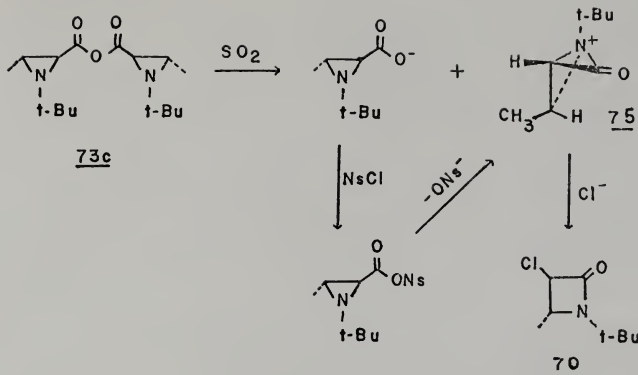
Chemical Shifts (δ) in Sulfur Dioxide Relative to External Tetramethylsilane in Carbon Tetrachloride

Substrate

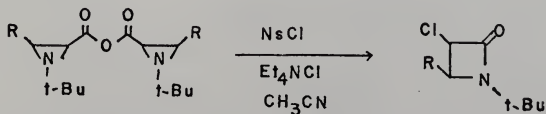


R	<u>66</u>	<u>75</u>	$\Delta\delta$ ppm*
t-Bu	0.62	0.88	0.26
CHCH	2.04	2.80	0.76
CH ₃	0.83	1.15	0.32

* Difference in chemical shifts of ester 66 and ion 75; it is apparent from Table IV that the methyl-2-aziridinecarboxylate is a legitimate model (nmr) for the 2-aziridine anhydride.



The ring expansion of the anhydride could also be effected in acetonitrile. Good yields of 3-chloro-2-azetidinones were obtained when the aziridine anhydrides (73a and 73b) and nosyl chloride were dissolved in a solution of excess tetraethyl ammonium chloride in acetonitrile.



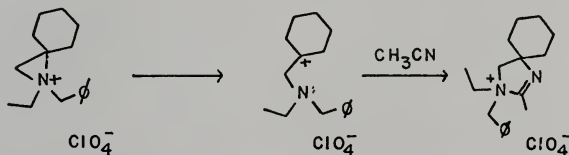
$\text{R} = \text{H};$ 73a

50 17%

$\text{R} = \text{CH}_3;$ 73b

69 75%

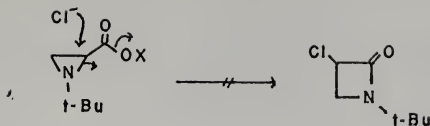
It is pertinent to this discussion that, although acetonitrile is a well established carbonium ion trap,⁵³ no detectable amount of ionic intermediate was intercepted. This is in accord with the observations of Leonard that aziridinium ions do not react directly with acetonitrile. Ring opening of aziridinium ion 76 to form a more stable carbonium ion occurs prior to reaction with acetonitrile.⁵⁴



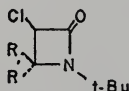
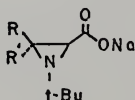
76

The postulated intermediate (58) is, among other things, an aziridinium ion and thus would not be expected to react with acetonitrile.

The ring expansion of the aziridine anhydrides convincingly rules out the possibility of any cyclic intermediate (54) such as discussed previously. The direct observation of the bicyclic ions (74 and 75) in sulfur dioxide rules out any concerted geitonodesmic⁵⁵ ring expansion of the anhydride.



The observed increase in yield of 2-azetidinone with methyl substitution at the 3-position in the reaction of the aziridine salts with oxalyl chloride is also not in accord with a geitonodesmic rearrangement.



$R = R' = H$; 53

50 26 %

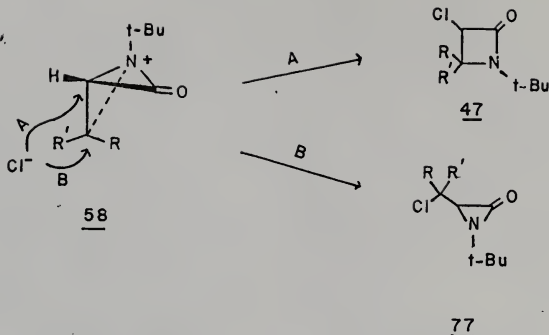
$R = CH_3$; $R' = H$; 67

69 79 %

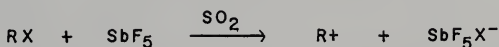
$R = H$; $R' = CH_3$; 68

70 63 %

This increase in yield may reflect steric inhibition of nucleophilic attack at the 4-position (route B) of the cation. Such attack, leading to α -lactam formation⁵⁶ (77), might compete with attack at the 3-position (route A) leading to 2-azetidinone formation. It would be interesting to see if the yield further increased with 3,3-dimethyl-2-aziridinecarboxylate. Similarly, one might predict substitution at the 2-position to inhibit 2-azetidinone formation.



It was thought that the 3-chloro-2-azetidinones might readily lend themselves to an nmr study in antimony pentafluoride-sulfur dioxide solution. Alkyl halides, when dissolved in this solution, ionize to give stable solutions of carbonium ions which can be observed by nmr spectroscopy.⁵⁷

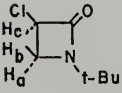


With this in mind, 1-t-butyl-3-chloro-2-azetidinone (50) was dissolved in a saturated solution of antimony pentafluoride in sulfur dioxide. The nmr spectrum of the resulting solution was compared to that of the azetidinone (50) in sulfur dioxide (relative to external TMS in CCl₄). Considerable downfield shifts were observed ($\Delta\delta$ ppm, Table VI) for the

antimony pentafluoride solutions, but little change in the splitting pattern was noted. Similar results were obtained with cis-1-*t*-butyl-3-chloro-4-methyl-2-azetidinone (69). The spectra of the antimony pentafluoride solutions are quite different from the sulfur dioxide spectra of the same supposed ions generated from the anhydride presursors. The changes in the chemical shift ($\Delta\delta$ ppm) are real and are reasonable for what one might expect for ammonium ion formation.* In fact, they are greater than the values of $\Delta\delta$ ppm observed for triethyl amine and tetraethyl ammonium chloride, a model system which neglects all anisotropic effects of the bicyclic rings (Table VI).

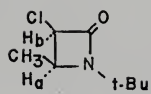
TABLE VI

Chemical Shifts (δ) Relative to External Tetramethylsilane
in Carbon Tetrachloride

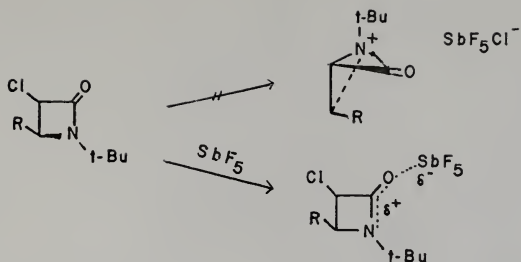
Compound	R	SO ₂	SO ₂ ·SbF ₅	$\Delta\delta$ ppm
	<i>t</i> -Bu	0.75	1.15	0.40
	Hc	4.08	4.89	0.81
	Hb	3.18	4.02	0.84
	Ha	2.70	3.59	0.89

* For hydrogens two carbons removed from a cation center shifts of 0.8-1.8 ppm are common.⁵⁸

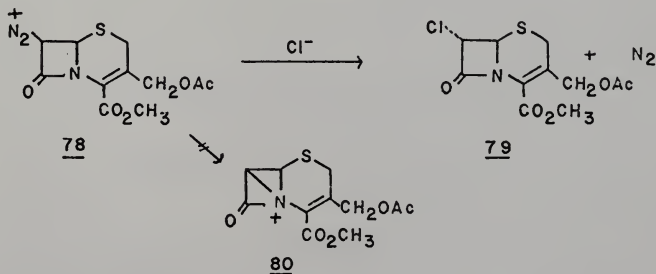
TABLE VI (cont'd)

Compound	R	SO ₂	SO ₂ ·SbF ₅	Δδ ppm
	t-Bu	0.76	1.08	0.32
	Hb	4.22	4.95	0.73
	Ha	3.56	4.37	0.81
	CH ₃	0.80	1.25	0.45
Et ₃ N	CH ₃	0.50		
	CH ₂	2.08		
Et ₄ NCl	CH ₃	0.69		0.19
	CH ₂	2.65		0.57

However, when attempts were made to quench these supposed ions with methanol according to procedures used by Olah⁵⁹ to quench similarly formed carbonium ions, only the original chloroazetidiones could be recovered. These results are interpreted as indicating donor-acceptor complex formation,⁶⁰ probably either with oxygen and/or nitrogen and antimony pentafluoride, but not ionization.



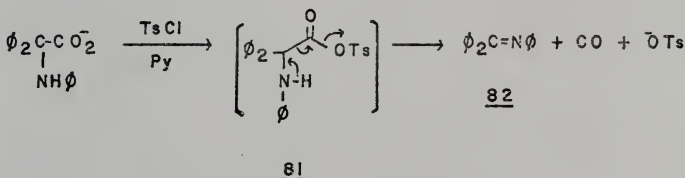
It is not surprising that ionization of the chloroazetidinones (47) fails to occur. Diazonium ion 78 recently has been generated in the cephalosporin series.⁶¹ This ion, in the presence of chloride, undergoes a displacement to form the chlorocephalosporin (79). The observed inversion of configuration suggests that the reaction of 78 does not proceed by loss of nitrogen to give the bicyclic ion (80). Formation and capture of 80 would require retention of configuration.



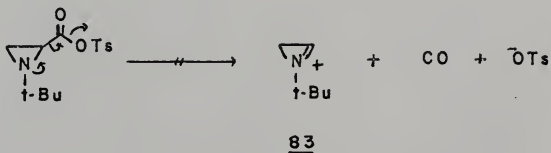
The reluctance of the 3-substituted-2-azetidinones to ionize to the bicyclic cations can be rationalized on stereochemical grounds. An examination of crude models shows that the unshared pair of electrons on nitrogen is

not oriented favorably for overlap at the incipient cation center. Considerable bond deformation, and hence strain, is required for participation and thus ionization to occur. Furthermore, the planar amide linkage would presumably inhibit such a deformation.

Formation of bicyclic cations (58) is in contrast to the ionization of the tosyl α -amino acid anhydride (81)* described by Sheehan and Frankenfeld.⁶² In that system fragmentation occurred to give the tosylate anion, a Schiff base (82), and carbon monoxide, presumably via participation of the electron pair on nitrogen.



The analogous reaction in the aziridine system would have generated the azirinium ion (83). Although such cations are known, they are greatly destabilized by ring strain.⁶³



* The mixed anhydride (81) was not isolated.

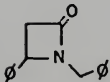
Attempts have been made to extend the ring expansion to aziridines with other substituents on nitrogen, but to no avail. Nevertheless, hope still remains that suitable conditions will be found to make this reaction more general and synthetically useful. The potential biochemical utility of the 2-azetidinones makes such a stereospecific synthesis quite valuable. No attempt has been made to extend the ring expansion to other heterocyclic rings. However the possibility of such extension is considered to be a matter of both synthetic and mechanistic interest.

Basic Hydrolysis of 3-Halo-2-Azetidinones

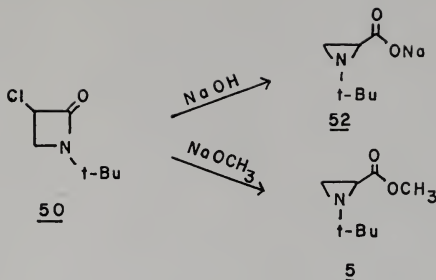
Basic hydrolysis of 2-azetidinones generally leads to high yields of β -amino acids. These reactions have received considerable attention in the literature.⁶⁴ A. D. Holley has found that the rate of hydrolysis is very much a function of the substituents on the ring, and it is presumed that this effect is the result of a combination of steric and inductive effects. As one might predict from strain arguments, the rates of hydrolysis for 2-azetidinones are greater than those for pyrrolidones, which in turn are greater than those for N-methylacetamide.⁶⁵

TABLE VII

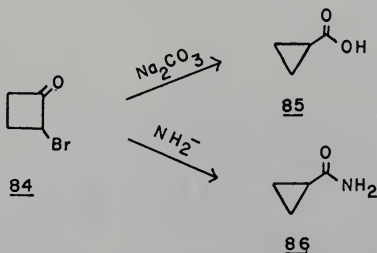
Apparent Second Order Rate Constants for Hydrolysis⁶⁴
(0.5 N NaOH/85% Ethanol, 50)

Compound	$10^{-2}k_2$ (liter/mole/sec)
	13.0
	1.0
	0.4
$\text{CH}_3\text{CONHCH}_3$	0.03

Basic hydrolysis of the 3-chloro-2-azetidinones (46) led not to the amino acids, but to the aziridinecarboxylic acid systems. 1-t-Butyl-3-chloro-2-azetidinone (50) gave good yields of sodium 1-t-butyl-2-aziridinecarboxylate (52) and methyl 1-t-butyl-2-aziridinecarboxylate (5) when treated with aqueous sodium hydroxide and with methanolic sodium methoxide respectively.

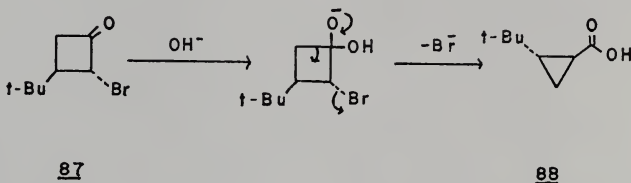


Similar ring contractions have been observed in the analogous carbocyclic system. For example, Conia and Ripoll⁶⁷ have treated α -bromocyclobutanone (**84**) with aqueous sodium carbonate and with sodium amide in liquid ammonia and recovered cyclopropanecarboxylic acid (**85**)⁶⁶ and cyclopropanecarboxamide (**86**),⁶⁷ respectively.

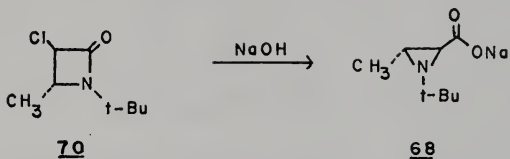
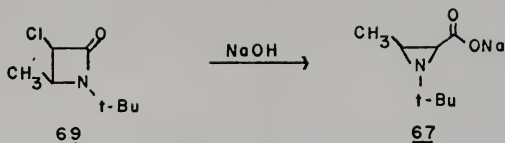


The mechanism proposed for these ring contractions involves initial attack of the base at the carbonyl carbon, followed by what is probably a concerted ring contraction giving the observed products.⁶⁸ The reaction is stereospecific as one might predict. Trans-2-bromo-3-*t*-butylcyclo-

butanone (87) when treated with aqueous sodium carbonate gives an approximately quantitative yield of trans-2-t-butylcyclopropanecarboxylic acid (88).⁶⁶

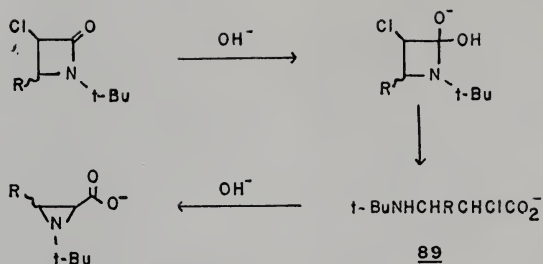


A mechanism similar to the above might be involved in the ring contraction of the 3-chloro-2-azetidinones. Attack of base at the carbonyl carbon probably occurs prior to ring contraction. No evidence is available which can unequivocally distinguish between a concerted or a nonconcerted ring contraction step. The ring contraction is stereospecific however. Cis-1-t-butyl-3-chloro-4-methyl-2-azetidinone (69) on treatment with sodium hydroxide in aqueous dioxane gave clean sodium cis-1-t-butyl-3-methyl-2-aziridinecarboxylate (67). Similarly, trans-1-t-butyl-3-chloro-4-methyl-2-azetidinone (70) gave the trans aziridine sodium salt (68) on treatment with base. In the latter case the reaction was not at all clean. The structures of the other products of the reaction (which comprise about 50% of the recovered material) were not determined, and thus it cannot be said with certainty that none of the cis salt (66) was formed. In spite of this it does follow that the ring contraction is stereospecific.



A dramatic difference was noted in the rates of hydrolysis of the various chlorazetidinones. No quantitative rate data are available, but it can be said that the 4-methyl-3-chloro-2-azetidinones hydrolyzed at a slower rate than the unsubstituted chlorazetidinone (20 vs 2 hr for complete reaction at reflux temperature). It is suspected that this difference is due to a similar combination of steric and electronic effects which plays so important a role in the hydrolysis of the azetidinones studies by Holley and Holley.⁶⁵

It might even be suggested that the rate controlling step of the ring contraction is hydrolysis to give the α -chloro- β -amino acid (89) which under the basic conditions employed ring closes stereospecifically to give the aziridine (Gabriel Synthesis).⁷ This might also explain the mixture of products observed for the ring contraction of trans-1-*t*-butyl-3-chloro-4-methyl-2-azetidinone. The intermediate amino acid (89) could conceivably lead to several products.

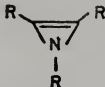


The ring contraction does suggest the possibility of a synthetically useful stereospecific route to the aziridine system. Extension of the reaction to azetidinones with different substituents, for instance aryl substituents, has not yet been attempted.

CHAPTER III

PYROLYSIS OF TRIPHENYLMETHYL 1-t-BUTYL-2-AZIRIDINECARBOXYLATE

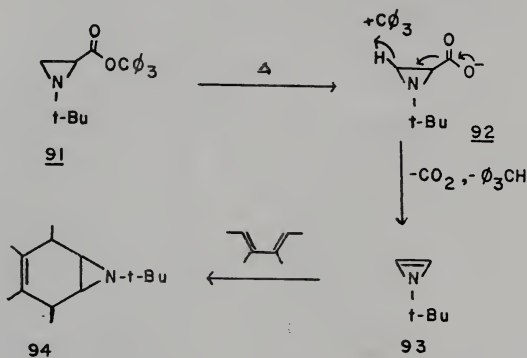
One of the more theoretically intriguing and yet still more elusive systems waiting to be synthesized is the 2-azirine system (90). It has been suggested that this cyclic class of compounds with potentially four pi electrons could be antiaromatic.⁶⁹ For this reason it might be expected to exhibit some rather interesting properties. A few unsubstantiated claims for 2-azirines can be found in the literature,^{7,70} but an authentic 2-azirine has yet to be isolated.



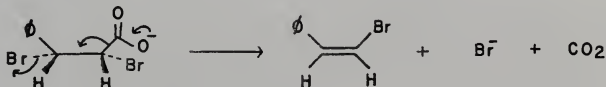
90

The hope of generating and studying a 2-azirine was the driving force behind the investigation of the pyrolysis of triphenylmethyl 1-t-butyl-2-aziridinecarboxylate (91). It was thought that heating this ester in a suitable solvent might induce ionization to form the triphenylmethyl cation and the carboxylate anion (92). Since the triphenylmethyl cation has been shown to be an effective hydride ion abstracting agent for hydrogen atoms α to the nitrogen in alkyl amines,⁷¹ it was hoped that hydride ion abstraction from the 3-position of the aziridinecarboxylate anion by the triphenylmethyl cation

generated in situ would occur with simultaneous or subsequent decarboxylation to produce the first member (93) of the long-sought 2-azirine system. With luck, this could be trapped with a diene to form a Diels-Alder adduct (94).⁷²

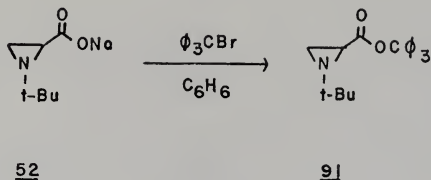


It might be noted that this proposed decarboxylation is quite analogous to the decarboxylation in acetone of the anion of cinnamic acid dibromide, an apparently trans E 2 elimination.⁷³

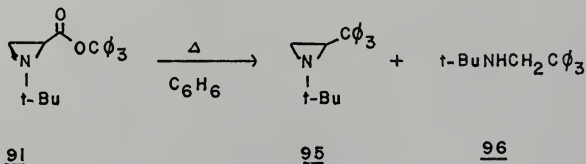


Triphenylmethyl esters of aziridine acids had not previously been prepared. Fortunately, published procedures for the formation of other triphenylmethyl esters from the sodium salts of the acids proved satisfactory.⁷⁴ Reaction of sodium 1-*t*-butyl-2-aziridinecarboxylate (**52**) with triphenylmethyl bromide in benzene gave the desired triphenylmethyl 1-*t*-butyl-2-aziridinecarboxylate (**91**) in a reasonable yield.

This ester was a solid and was quite stable when in a pure state.

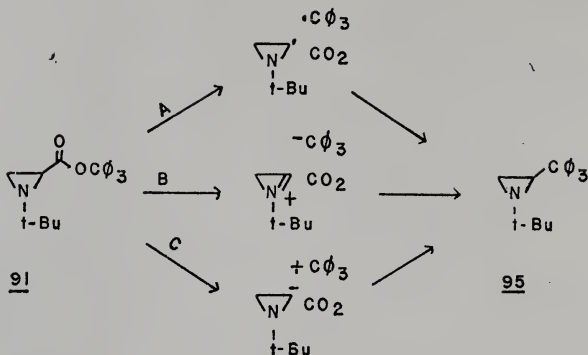


The ester (91) was heated in a sealed tube in benzene at $180 \pm 10^\circ$ for fourteen hours. When the tube was cooled and opened, a noticeable amount of pressure was released, suggestive of gas evolution (decarboxylation). Two major components, representing about 90% of the reaction were recovered from the reaction mixture and characterized as 1-t-butyl-2-triphenylmethylaziridine (95, 57%) and N-t-butyl-triphenylmethylmethanamine (96, 33%).

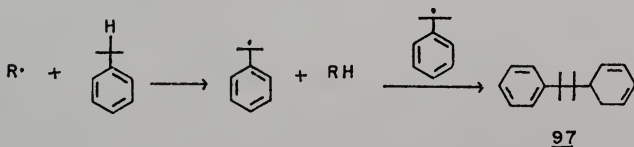


These products were not suggestive of 2-azirine formation. Nevertheless the problem of the mechanism of formation of both products was considered intriguing. Several routes for decarboxylation to the triphenylmethylaziridine are possible, one radical (A) and two ionic (B and C). Formation of the amine (96) was unclear. A control experiment showed that the triphenylmethylaziridine (95) was stable to the

reaction conditions and thus is not the source of the amine (96).



Decarboxylation of triphenylmethyl esters via a radical path has been suggested before although the data presented did not serve to unequivocally demonstrate the existence of radicals.⁷⁵ The possibility of a radical path in this aziridine system was investigated by carrying out the pyrolysis in cumene, a known and effective radical trap. Radicals abstract a hydrogen atom from cumene to form a cumyl radical which then couples with another similarly formed cumyl radical to form dicumyl (97). Thus the presence of dicumyl is evidence for the presence of radicals.⁷⁶



Conversely, the absence of dicumyl suggests that radicals are not present. Nevertheless it is conceivable that cage recombination of the radicals is so efficient that intervention of the radical scavenging cumene cannot occur.⁷⁷

The pyrolysis in cumene gave a practically identical product distribution as pyrolysis in benzene, and no detectable dicumyl was formed. Analysis for dicumyl was done by gas chromatography, and it was estimated that as little as 1% of the theoretical amount of dicumyl would be detected. Thus the radical mechanism was deemed unlikely.

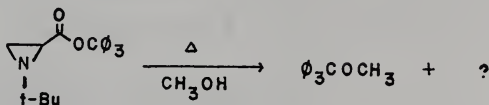
Studies of the decarboxylation of carboxylic acids indicate that generally decarboxylation occurs to form the carbanion. The reaction is facilitated by groups which stabilize the carbanion centers, for instance electronegative heteroatoms. No example of carbonium ion formation via decarboxylation of carboxylic acids is known.⁷⁸



Thus it might be expected that decarboxylation of the ester (91) is occurring via ionization to the triphenylmethyl cation, followed by decarboxylation to form the aziridine carbanion (Path C). The problem was to experimentally verify this prediction.

It was thought that a distinction between the two ionic paths (B and C) might be made via a trapping experiment. For this reason the triphenylmethyl ester (91) was pyrolyzed in methanol. It was predicted that methanol would intercept the carbonium ion to form a methyl ether. The carbanion should pick up a proton. After pyrolysis methyl

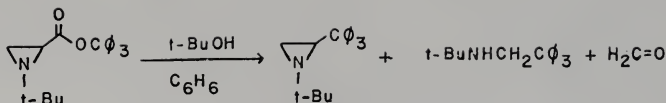
triphenylmethyl ether was recovered, indicating that ionization to give the triphenylmethyl carbonium ion had occurred. Unfortunately no other species were recovered from the complex reaction mixture.



91

Since no aziridine fragment was recovered, and since the change in the solvent was so drastic, it is not valid to claim that the decarboxylation occurs necessarily by path C merely on the basis of this experiment. It is felt that formation of methyl triphenylmethyl ether is at least supporting evidence for ionization as indicated in path C.

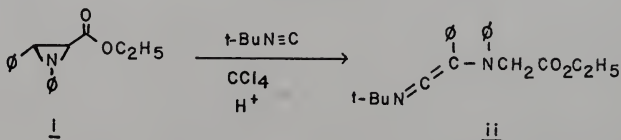
Addition of a proton source to the reaction medium should allow capture of the carbanion to give either triphenylmethane (path B) or 1-t-butylaziridine (path C). t-Butanol was chosen as the proton source because, although it was capable of protonating the carbanion, it is not a good enough nucleophile to cause transesterification or hydrolysis of the triphenylmethyl ester. Pyrolysis in benzene in the presence of one equivalent of t-butanol resulted in a clean reaction yielding the triphenylmethylaziridine (95, 11%) and N-t-butyl triphenylmethylmethylamine (96, 88%). In addition, when the benzene solution of the reaction mixture was washed with water and the water wash treated with dimedone reagent, the solid dimedone derivative (98) of formaldehyde was recovered.⁷⁹

969195

Although this experiment did not serve to differentiate between the two ionic routes to the triphenylmethylaziridine, it did suggest an explanation for the formation of the secondary amine, which in turn sheds much light on this system.

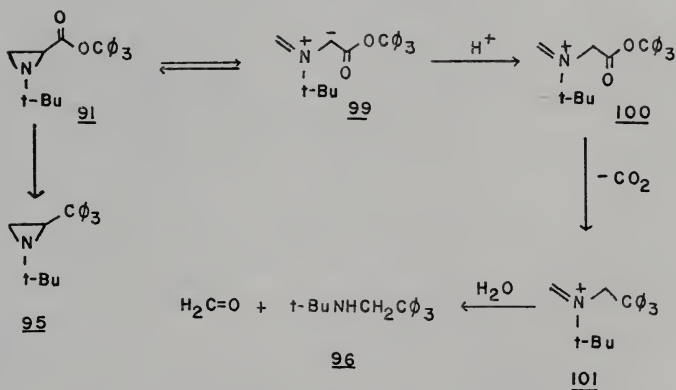
A most reasonable mechanism for the formation of N-t-butyl triphenylmethylmethanamine (96) involves formation of a 1,3-dipolar species (99). There are numerous examples where the aziridine ring opens to form a 1,3-dipolar species in this sense.⁸⁰ When protons are present in the system this dipolar species can be protonated* to give the iminium cation

* Precedent for protonation of an aziridine 1,3-dipole is claimed in the reaction of ethyl trans-1,3-diphenyl-2-aziridinecarboxylate (i) with t-butylisocyanide in acidic carbon tetrachloride to give a ketenimine (ii); J. A. Deyrup, to be published.



(100).⁸¹ Because of the positive charge on the nitrogen this ion should decarboxylate readily via an ionic route⁷⁸ to give a new iminium ion

(101). Hydrolysis of this ion would generate the amine 105 and formaldehyde, the observed products. If the dipolar species (99) is in equilibrium with the ester, the triphenylmethylaziridine (95) arises from the ester, and the amine (96) and formaldehyde arise from the 1,3-dipole as suggested, the addition of t-butanol would tend to intercept the dipolar species and give the observed product distribution.



If the decarboxylation yielding the triphenylmethylaziridine (95) is indeed proceeding via an aziridine carbanion, as is postulated here, it should be possible to generate analogous aziridine carbanions by other routes. If such procedures can be worked out they should be valuable as still another route to variously substituted aziridines.

CHAPTER IV

EXPERIMENTAL

The melting points were determined on a Thomas Hoover Capillary Melting Point Apparatus and are uncorrected. Boiling points are recorded as the temperature at which the material distills, are at atmospheric pressure unless otherwise noted, and are uncorrected. Evaporative distillations were performed on small samples of material following the (Kugelrohr) procedure of Graeve and Wahl.⁸²

The infra-red spectra were recorded on a Perkin-Elmer instrument, Model number 137.

The routine nmr spectra were recorded on a Varian Associates A-60-A 60 megacycle recording spectrometer. The nmr data are presented as follows: chemical shift (splitting pattern,^{*} number of hydrogens, coupling constant, assignment). Chemical shifts are expressed in parts per million and in carbon tetrachloride and chloroform are relative to internal tetramethylsilane. In deuterium oxide chemical shifts are relative to a position 4.99 ppm upfield from the DOH signal.⁴⁰ In sulfur dioxide chemical shifts are relative to external tetramethylsilane in carbon tetrachloride.

* s = singlet; d = doublet; dd = doublet of doublets; t = triplet; q = quartet; m = multiplet.

Molecular weights were determined by mass spectrometry. The mass spectra were recorded on a RMU 6E mass spectrometer at 70 ev. The fragments are reported as m/e (relative intensity).

Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee, and by Peninsula Chemresearch, Gainesville, Florida.

2,3-Dibromobutyric Acid

This was prepared according to the procedure of Michael and Norton.⁸³

2,3-Dibromobutyryl Chloride

Thionyl chloride (130 g, 1.1 mol) was added to 2,3-dibromobutyric acid (181 g, 0.74 mol) and the resulting solution was gently refluxed for three hours. Distillation yielded 167 g (86%) of the acid chloride: bp 95-100 (20 mm) [Lit. 112° (20 mm)];⁸⁴ nmr (CCl₄) δ 1.95 (d, 3, J = 6 Hz, CH₃), and 4.49 (m, 2, CHBrCHBr).

Methyl 2,3-Dibromobutyrate

2,3-Dibromobutyryl chloride (167 g, 0.635 mol) was added slowly to methanol (32 g, 1.0 mol) at room temperature with stirring. After ten minutes, excess methanol and hydrochloric acid were removed by rotary evaporation, and the residual oil was distilled to give 158 g (96%) of methyl 2,3-dibromobutyrate: bp 103-106° (17mm) [Lit. 125° (48 mm)];⁸⁴ nmr (CCl₄) δ 1.90 (m, 3, CH₃), 3.80 (s, 3, OCH₃), and 4.38 (m, 2, CHBr-CHBr).

Methyl 1-t-Butyl-2-Aziridinecarboxylate (5)

This was prepared according to the procedure of C. L. Moyer.⁴⁰

Methyl 1-Benzyl-2-Aziridinecarboxylate (12)

Methyl 2,3-dibromopropionate (39.0 g, 0.15 mol) was dissolved in benzene (300 ml) in a three-necked flask equipped with an overhead stirrer, dropping funnel, and condenser, and the flask was immersed in an ice bath. Triethylamine (45 g, 0.45 mol) was added in a dropwise fashion followed by benzylamine (16 g, 0.15 mol). The reaction mixture was refluxed overnight, then cooled to room temperature, and the solid amine hydrobromides were removed by filtration. Distillation of the thick oil left after evaporation of the filtrate gave 22.7 g (79%) of methyl 1-benzyl-2-aziridinecarboxylate (12): bp 90-95° (0.3 mm) [Lit. 133° (5mm)];⁸⁵ ir (liquid film) 1745 (C = O), 753, and 696 cm⁻¹ (phenyl); nmr (CCl₄) δ 1.50 (dd, 1, ring proton), 2.02 (m, 2, ring protons), 3.41 (q, 2, ϕCH_2), 3.56 (s, 3, OCH_3), and 7.20 (s, 5, C_6H_5).

Anal. Calcd for C₁₁H₁₃NO₂: C, 69.09; H, 6.85; N, 7.32.

Found: C, 69.08; H, 7.03; N, 7.20.

Methyl 1-Phenyl-2-Aziridinecarboxylate (7)

Methyl 2,3-dibromopropionate (74 g, 0.28 mol) was dissolved in benzene (200 ml) and cooled in an ice bath. Triethylamine (63 g, 0.7 mol) was added dropwise to the stirred solution as triethylamine hydrobromide precipitated. Then aniline (28 g, 0.3 mol) was added,

and the reaction mixture was refluxed gently for 12 hours. The amine hydrobromides were removed by filtration, and the crude oil left after evaporation was distilled to give 34.6 g (69%) of methyl 1-phenyl-2-aziridinecarboxylate (7): bp $92-100^{\circ}$ (0.5 mm) [Lit. $95-105^{\circ}$ (0.3 mm)];¹⁹ ir (liquid film) 1750 (C = O), 754, and 695 cm^{-1} (phenyl); nmr (CCl_4) δ 2.1 (dd, 1, ring proton), 2.6 (m, 2, ring protons), 3.62 (s, 3, OCH_3), and 7.0 (m, 5, C_6H_5).

Anal. Calcd for $\text{C}_{10}\text{H}_{11}\text{NO}_2$: C, 67.78; H, 6.26; N, 7.90.

Found: C, 67.73; H, 6.35; N, 7.86.

Methyl *Cis*-1-t-Butyl-3-Methyl-2-Aziridinecarboxylate (65)

Methyl 2, 3-dibromobutyrate (100 g, 0.38 mol), triethylamine (100 g, 0.96 mol), and methanol (400 ml) were stirred at room temperature for three hours. t-Butylamine (70 g, 0.96 mol) was added, and the mixture was allowed to stand at room temperature for two days. Water was added, and the solution was extracted two times with benzene, dried (MgSO_4), and evaporated to an oil which on distillation gave 50 g (78%) of a mixture of *cis*-1-t-butyl-3-methyl-2-aziridinecarboxylate (65, 85%) and *trans*-1-t-butyl-3-methyl-2-aziridinecarboxylate (66, 15%). The pure *cis* isomer was obtained by spinning band distillation: bp 65° (3.0 mm); ir (liquid film) 2900 (CH) and 1750 cm^{-1} (C = O); nmr (CCl_4 ; spectrum No 1) δ 0.95 (s, 9, t-butyl), 1.17 (d, 3, $J = 5.3\text{ Hz}$, CH_3), 2.05 (m, 2, CHCH), and 3.65 (s, 3, OCH_3); molecular weight 171.

Anal. Calcd for $\text{C}_9\text{H}_{17}\text{NO}_2$: C, 63.13; H, 10.01; N, 8.18.

Found: C, 63.03; H, 9.99; N, 7.95.

Methyl Trans-1-t-Butyl-3-Methyl-2-Aziridinecarboxylate (66)

Methyl 2,3-dibromobutyrate (26 g, 0.10 mol) and triethylamine (39 g, 0.015 mol) were dissolved in benzene (50 ml) and left at room temperature overnight. The amine hydrobromides were removed by filtration, and the filtrate was evaporated to an oil. The oil was dissolved in t-butylamine (18.2 g, 0.25 mol) and left at room temperature for four days. The amine hydrobromides were removed by filtration, and the filtrate was evaporated to an oil which on distillation gave 12.4 g (72%) of a mixture of cis-(33%) and trans-(67%) methyl 1-t-butyl-3-methyl-2-aziridinecarboxylate. The trans isomer (66) was, after washing with aqueous sodium carbonate, completely separated from the cis isomer by spinning band distillation: bp 65° (0.2 mm); ir (liquid film) 2950 (CH) and 1730 cm^{-1} (C = O); nmr (CCl_4 ; spectrum No 2) δ 1.10 (s, 9, t-butyl), 1.26 (d, 3, J = 5.5 Hz, CH_3), 2.13 (d, 1, J = 2.4 Hz, C_2H), 2.46 (m, 1, C_3H), 3.63 (s, 3, OCH_3); molecular weight 171.

Anal. Calcd for $\text{C}_9\text{H}_{17}\text{NO}_2$: C, 63.13; H, 10.01; N, 8.18.

Found: C, 63.44; H, 10.14; N, 8.31.

Reaction of 1-t-Butyl-2-Aziridinecarboxylate (5) With
Hydrazine Hydrate in Ethanol

Methyl 1-t-butyl-2-aziridinecarboxylate (5, 1.61 g, 0.01 mol) and hydrazine hydrate (1.0 g, 0.02 mol) were added together with enough ethanol (1 ml) to effect solution. The solution was refluxed for five

* This is a standard procedure for making carboxylic acid hydrazides. ¹⁸

hours, cooled to room temperature, and the solvent was evaporated. Evaporative distillation of the residual oil gave 0.91 g (65%) of 3-t-butylaminopropionic acid hydrazide (6): bp 100° (0.1 mm); ir (nujol) 3140 (NH) and 1655 cm^{-1} (C = O); nmr (D_2O) δ 2.25 (s, 9, t-butyl), 2.54 (m, 2, CH_2), and 2.99 (m, 2, CH_2); molecular weight 159.

Anal. Calcd for $\text{C}_7\text{H}_{17}\text{N}_3\text{O}$: C, 52.80; H, 10.76; N, 26.39.

Found: C, 51.56; H, 10.50; N, 26.17.

1-t-Butyl-2-Aziridinecarboxylic Acid Hydrazide (9)

Methyl 1-t-butyl-2-aziridinecarboxylate (5, 1.57 g, 10.0 mmol) and hydrazine hydrate (0.45 g, 9.0 mmol) were stirred at room temperature for 9.5 hours. The resulting oil was then triturated with cyclohexane. Residual cyclohexane was then removed by evaporation in vacuo to give a clear oil. Nmr observation of the oil indicated that 89% of the t-butyl containing species present was the aziridine hydrazide (9). Also present were some methanol and starting ester: nmr (D_2O ; spectrum No 5) δ 1.26 (s, 9, t-butyl), 2.17 (m, 2, ring protons), and 2.64 (dd, 1H, ring proton).

1-Benzyl-2-Aziridinecarboxylic Acid Hydrazide (13)

Methyl 1-benzyl-2-aziridinecarboxylate (12, 15 g 0.078 mol) and hydrazine hydrate (3.85 g, 0.077 mol) were stirred together at room temperature for 40 minutes. The reaction mixture was then seeded with a small crystal of 13, and the reaction mixture solidified to a cake. Attempted recrystallization from benzene caused some decomposition. The reaction mixture was dissolved in hot benzene, treated with de-

colorizing charcoal, and cooled. After filtration 9.7 g (66%) of colorless crystals were recovered and identified as 1-benzyl-2-aziridinecarboxylic acid hydrazide (13): mp 92-96° dec; ir (nujol) 3200 (NH), 1650 (C = O), 730, and 693 cm^{-1} (phenyl); nmr (CDCl_3 ; spectrum No 6) δ 1.79 (m, 1, ring proton), 1.97 (m, 1, ring proton), 2.25 (dd, 1, ring proton), 3.5 (s, 2, OCH_2), 3.65 (broad, 3, N_2H_3), and 7.31 (s, 5, C_6H_5); molecular weight 191.

The 1-benzyl-2-aziridinecarboxylic acid hydrazide (13) was characterized as the acetone hydrazone 15.

1-Phenyl-2-Aziridinecarboxylic Acid Hydrazide (14)

Methyl 1-phenyl-2-aziridinecarboxylate (12, 10.78 g, 0.06 mol) and hydrazine hydrate (3.0 g, 0.06 mol) were stirred together at room temperature for one hour. Benzene (25 ml) was added and removed by evaporation in vacuo. Ether (25 ml) was added and a solid formed which was then washed with ether to give 5.8 g (54%) of the aziridine hydrazide (14): mp 67-75° dec; ir (nujol) 3220 (NH), 1670 (C = O), 760, and 693 cm^{-1} (phenyl); nmr (CDCl_3 ; spectrum No 7) δ 2.32 (m, 2, ring protons), 2.78 (dd, 1, ring proton), 4.05 (broad, 3, N_2H_3), and 7.05 (m, 5, C_6H_5); molecular weight 177.

The 1-phenyl-2-aziridinecarboxylic acid hydrazide (14) was characterized as the acetone hydrazone 16.

1-Benzyl-2-Aziridinecarboxylic Acid Hydrazide-Acetone Hydrazone (15)

Methyl 1-benzyl-2-aziridinecarboxylate (12, 1.83 g, 9.5 mmol) and hydrazine hydrate (0.478 g, 9.5 mmol) were stirred together and warmed

on a steam bath for ten minutes. A white cake formed which was then dissolved in acetone (10 ml). After about ten minutes 2.2 g (70%) of colorless crystals of the hydrazone (15) precipitated. They were recrystallized from methanol: mp 143-144°; ir (nujol) 1780 (C = O), 1665, (C = N), 730, and 695 cm^{-1} (phenyl); nmr (CDCl_3 ; spectrum No 8) δ 1.79 (s, 3, CH_3), 1.95 (m, 2, ring protons), 2.04 (s, 3, CH_3), 2.35 (dd, 1, ring proton), 4.55 (q, 2, OCH_2), and 7.31 (s, 5, C_6H_5); molecular weight 231.

Anal. Calcd for $\text{C}_{15}\text{H}_{17}\text{N}_3\text{O}$: C, 67.51; H, 7.41; N, 18.17.

Found: C, 67.59; H, 7.41; N, 18.21.

1-Phenyl-2-Aziridinecarboxylic Acid Hydrazone-Acetone
Hydrazone (16)

1-Phenyl-2-aziridinecarboxylic acid hydrazone (14, 0.2 g, 1.0 mmol) was dissolved in acetone (7 ml) at room temperature. In about five minutes 0.17 g (70%) of the hydrazone (16) precipitated. It was recrystallized from methanol: mp 161-174° dec; ir (nujol) 3113 (NH), 1690, 1670, and 1640 cm^{-1} (C = O and C = N); nmr (CDCl_3 ; spectrum No 9) δ 1.85 (s, 3, CH_3), 2.09 (s, 3, CH_3), 2.31 (m, 2, ring proton), 2.89 (dd, 1, ring proton), and 7.1 (m, 5, C_6H_5): molecular weight 217.

Anal. Calcd for $\text{C}_{12}\text{H}_{15}\text{N}_3\text{O}$: C, 66.34; H, 6.96; N, 19.34.

Found: C, 66.49; H, 7.05; N, 19.39.

Reaction of 1-t-Butyl-2-Aziridinecarboxylic Acid Hydrazone
(9) With Water

Methyl 1-t-butyl-2-aziridinecarboxylate (5, 1.57 g, 10.0 mmol) and hydrazine hydrate (0.48 g, 9.5 mmol) were stirred for nine hours at room temperature. The resulting oil, crude 1-t-butyl-2-aziridine-

carboxylic acid hydrazide (9), was then refluxed overnight in water (15 ml). The resulting reddish brown solution was cooled to room temperature and concentrated. On standing overnight 0.2 g (15%) of 3-t-butylaminopropionic acid (11) precipitated and was identified by comparison of ir and nmr spectra and mixed melting point with an authentic sample.

3-t-Butylaminopropionic Acid (11)^{*}

t-Butylamine (3.65 g, 0.05 mol) was added to a solution of acrylic acid (3.60 g, 0.05 mol) in pyridine (10 ml). Evolution of heat and the instantaneous formation of a colorless solid were observed. The mixture was then refluxed for three hours. The solution was allowed to cool to room temperature, and the solvent was removed by rotary evaporation. The residue was washed with acetone to give 5.68 g (79%) of 3-t-butylaminopropionic acid (11); mp 229-230°; ir (nujol) 3300 (NH), 1630 and 1540 cm^{-1} (C = O); nmr (D_2O) δ 1.64 (s, 9, t-butyl), 2.84 (m, 2, CH_2) and 3.54 (m, 2, CH_2); molecular weight 145.

Anal. Calcd for $\text{C}_7\text{H}_{17}\text{N}_3\text{O}$: C, 52.80; H, 10.76; N, 26.39.

Found: C, 51.56; H, 10.50; N, 26.17.

Thermal Decomposition of 1-t-Butyl-2-Aziridinecarboxylic
Acid Hydrazide (9)

Methyl 1-t-butyl-2-aziridinecarboxylate (5, 314 g, 0.02 mol) and hydrazine hydrate (1.0 g, 0.02 mol) were mixed and allowed to sit at room temperature for five days. A colorless solid precipitated which after recrystallization from ethanol gave 0.36 g (13%) of 1,2-di-3-t-

^{*}This synthesis was patterned after the synthesis of an analogous β -amino acid.⁸⁰

butylaminopropionyl hydrazine (10): mp 159-160°; ir (nujol) 3075 (NH), 1690 and 1685 cm^{-1} (C = O); nmr (D_2O) δ 1.34 (s, 9, t-butyl), 2.67 (m, 2, CH_2), and 3.17 (m, 2, CH_2); molecular weight 286.

Anal. Calcd for $\text{C}_{14}\text{H}_{30}\text{N}_4\text{O}_2$: C, 58.71; H, 10.56; N, 19.56.

Found: C, 58.81; H, 10.22; N, 19.36.

Fragmentation of 1-t-Butyl-2-Aziridinecarboxylic Acid
Hydrazide (9) in the Presence of Azobenzene

A solution of azobenzene (0.84 g, 4.6 mmol) in methanol was added to a solution of 1-t-butyl-2-aziridinecarboxylic acid hydrazide (9, 1.5 g, 9.0 mmol) in methanol (25 ml) at room temperature. The resulting solution was refluxed overnight. Tlc (benzene/alumina) showed disappearance of azobenzene and appearance of hydrazobenzene. When the solution was concentrated, 0.22 g (26%) of crystals precipitated and were identified as hydrazobenzene after washing with cyclohexane: mp 120-124° (Lit. 125-126).⁸⁷

The filtrate was evaporated to a solid which after washing with ether yielded 0.1 g (8%) of 3-t-butylaminopropionic acid (11).

Thermal Decomposition of 1-Benzyl-2-Aziridinecarboxylic
Acid Hydrazide (13) in Water

1-Benzyl-2-aziridinecarboxylic acid hydrazide (13, 0.4 g, 2.0 mmol) was dissolved in water and refluxed for three hours, then cooled to room temperature and extracted with ether. The water layer was evaporated to precipitate colorless crystals which were recrystallized from methanol to give 0.1 g (26%) of 3-benzylaminopropionic acid (17). This was iden-

tified by comparison of ir spectra and mixed melting point with an authentic sample.

3-Benzylaminopropionic Acid (17)⁸⁶

Acrylic acid (3.6 g, 0.05 mol) and benzylamine (5.3 g, 0.05 mol) were refluxed in pyridine for three hours, then cooled to room temperature. On standing, 3.8 g (42%) of 3-benzylaminopropionic acid (17) precipitated. This was recrystallized from methanol: mp 182-186°; (Lit. 182-183°);⁸⁸ ir (nujol) 1630, 1570 (C = O), 750, and 700 cm⁻¹ (phenyl); nmr (D₂O) δ 2.87 (t, 2, CH₂), 3.55 (t, 2, CH₂), 4.54 (s, 2, ϕ CH₂) and 7.80 (s, 5, C₆H₅).

Thermal Decomposition of 1-Benzyl-2-Aziridinecarboxylic Acid Hydrazide (13) in Methanol

A solution of 1-benzyl-2-aziridinecarboxylic acid hydrazide (13, 1.0 g, 5.0 mmol) was refluxed overnight in methanol (25 ml). The solution was cooled to room temperature and evaporated to an oil which on distillation gave 0.37 g (37%) of methyl 3-benzylaminopropionate (18): bp 90° (0.5 mm). An aliquot of the oil was dissolved in anhydrous ether (25 ml), and dry HCl gas was bubbled through the solution to precipitate the hydrochloride (19) of methyl 3-benzylaminopropionate. This was recrystallized from ethanol to give colorless needles: mp 159-160°. Identification was made by comparison of ir and nmr spectra and mixed melting points with an authentic sample.

Methyl 3-Benzylaminopropionate (18)

Benzylamine (6.22 g, 0.058 mol) was added to a solution of methyl acrylate (5.0 g, 0.058 mol) in methanol (50 ml), and the solution was allowed to sit at room temperature overnight. Methanol was removed by evaporation to give 11.2 g (100%) of methyl 3-benzylaminopropionate (18). Dry HCl was bubbled through a solution of 18 in anhydrous ether to precipitate the hydrochloride (19) of methyl 3-benzylaminopropionate. This was recrystallized from ethanol: mp 155-157° (Lit. 155-156°);⁸⁹ ir (nujol) 1738 (C = O), 764 and 696 cm⁻¹ (phenyl); nmr (D₂O) δ 3.21 (t, 2, CH₂), 3.68 (t, 2, CH₂), 4.07 (s, 3, CH₃), 4.62 (s, 2, OCH₂), and 7.83 (s, 5, C₆H₅); molecular weight 206.

Fragmentation of 1-Benzyl-2-Aziridinecarboxylic Acid Hydrazide (13)
in the Presence of Azobenzene

1-Benzyl-2-aziridinecarboxylic acid hydrazide (13, 0.89 g, 4.6 mmol) was added to a solution of azobenzene (0.25 g, 1.4 mmol) in methanol (25 ml) and refluxed for six hours. Tlc (benzene/alumina) showed the disappearance of azobenzene and the appearance of hydrazobenzene. The solution was evaporated to an oil. Thick layer chromatography (benzene/alumina) gave 0.33 g of a mixture of azobenzene and hydrazobenzene and 0.40 g (45%) of methyl 3-benzylaminopropionate (18).

The mixture of azobenzene and hydrazobenzene was column chromatographed (benzene/alumina) to give 0.085 g (9%) of hydrazobenzene which was recrystallized from methanol: mp 125-127° (Lit. 126-127°).⁸⁷

3-Anilinopropionic Acid Hydrazide (8)

1-Phenyl-2-aziridinecarboxylic acid hydrazide (14, 0.90 g, 4.7 mmol) was dissolved in a solution of hydrazine hydrate (10 ml) in ethanol (10 ml) and refluxed for one hour. The solvent was evaporated to give an oil. Benzene (10 ml) was added and evaporated to give 0.87 g (92%) of crystalline 3-anilinopropionic acid hydrazide (8). This was recrystallized from benzene: mp 89-90° (Lit. 95-96°);¹⁹ ir (nujol) 3225 (NH), 1638 (C = O), 744 and 643 cm⁻¹ (phenyl); nmr (D₂O) δ 2.78 (t, 2, J = 7 Hz, CH₂), 3.72 (t, 2, J = 7 Hz, CH₂), 7.4 (m, 5, C₆H₅); molecular weight 179.

1,2-Diphenylaziridine (21)

This was prepared according to the procedure of E. J. Corey and M. Chaykovsky.⁹⁰

1-t-Butyl-2-Aziridinecarbinol (22)

This was prepared according to the procedure of C. L. Moyer.⁴⁰

Ethyl Benzylaminoacetate

This synthesis was patterned after a procedure by Speziale and Jaworski.⁹¹ Ethyl chloroacetate (24.4 g, 0.2 mol) was added dropwise with stirring to an ice cooled solution of triethylamine (20.2 g, 0.2 mol) and aniline (21.4 g, 0.2 mol) in benzene (130 ml). The temperature was not allowed to exceed 5° during the addition. After addition was complete the reaction mixture was stirred at room temperature for one hour. Then potassium iodide (2.0 g) was added, and the reaction

mixture was refluxed overnight. It was then allowed to cool to room temperature and washed with aqueous sodium carbonate and then water. The benzene was removed by evaporation, and the residual oil was distilled to give 25.8 g (67%) of ethyl benzylaminoacetate: bp $91-95^{\circ}$ (0.2 mm) [Lit. 165° (16 mm)];⁹² ir (liquid film) 3250 (NH), 1740 (C = O), 740 and 700 cm^{-1} (phenyl); nmr (CCl_4) δ 1.2 (t, 3, CH_3), 1.76 (broad, 1, NH), 3.25 (s, 2, CH_2), 3.70 (s, 2, CH_2), 4.1 (q, 2, CH_2CH), and 7.2 (s, f, C_6H_5).

Benzylaminoacetic Acid Hydrazide (23)

Ethyl benzylaminoacetate (6.0 g, 0.03 mol) was stirred neat with hydrazine hydrate (2.0 g, 0.04 mol). The heterogeneous mixture was warmed on a steam bath for three minutes, then stirred at ambient temperature for one hour as the mixture become homogeneous. A seed was added and a colorless cake formed. The cake was recrystallized from isopropanol to give 3.62 g (65%) of benzylaminoacetic acid hydrazide (23): mp $80-82^{\circ}$ (Lit $82-84^{\circ}$);⁹³ ir (nujol) 3245 (NH), 1645 (C = O), 745 and 700 cm^{-1} (phenyl); nmr (CDCl_3) δ 3.5 (broad, 3, N_2H_3), 3.30 (s, 2, CH_2), 3.72 (s, 2, CH_2), and 7.29 (s, 5, C_6H_5); molecular weight 179.

Anilinoacetic Acid Hydrazide (24)

Hydrazine hydrate (4.0 g, 0.08 mol) was added to a solution of ethyl anilinoacetate (3.58 g, 0.02 mol). The mixture formed a solid cake within a few minutes. Ethanol (20 ml) was added, and the mixture was refluxed for two hours. Colorless plates precipitated on cooling. They were recrystallized from ethanol to give 2.95 g (89%) anilino

acetic acid hydrazide (24): mp 125-126.5° (Lit. 126.5°);⁹⁴ ir (nujol) 3280 (NH), 1650 (C = O), 745 and 685 cm⁻¹ (phenyl); nmr (D₂O) δ 4.09 (s, 2, CH₂), and 7.25 (m, 5, C₆H₅).

1,2-Diphenylaziridine (21)-Stability to Hydrazine Hydrate

1,2-Diphenylaziridine (21, 0.95 g, 5.0 mmol) and hydrazine hydrate (0.04 g, 7.0 mmol) were mixed together with enough methanol (4 ml) to effect solution. The solution was left at room temperature for four days. Solvent was removed by evaporation. An nmr spectrum of the residue indicated that no reaction had occurred.

1-t-Butyl-2-Aziridinecarbinol (22)-Stability to Hydrazine Hydrate

Hydrazine hydrate (0.71 g, 15.0 mmol) was added to 1-t-butyl-2-aziridinecarbinol (22, 0.96 g, 7.5 mmol) and enough methanol to effect solution. The solution was left at room temperature for four days. Solvent was removed by evaporation. An nmr spectrum of the residue indicated that no reaction had occurred.

Benzylaminoacetic Acid Hydrazide (23)-Stability to Methanol

Benzylaminoacetic acid hydrazide (23, 0.57 g, 3.2 mmol) was refluxed in methanol (25 ml) for 24 hours. Tlc (chloroform-methanol/alumina) indicated that no reaction had taken place. Solvent was removed by evaporation. The residual oil was taken up in 2-propanol, and the resulting solution, when seeded, yielded 0.54 g (95%) of 23: mp 80-82°.

Anilinoacetic Acid Hydrazide (24)-Stability to Methanol

Anilinoacetic acid hydrazide (24, 0.54 g, 3.27 mmol) was refluxed in methanol (25 ml) for 24 hours. Tlc (chloroform/alumina) indicated that no reaction had occurred. Solvent was removed by evaporation to give 0.59 g, (100%) of 24: mp 124-126.5°.

Ethyl β , β -Tetramethyleneglycidate*

In a flame dried apparatus ethyl chloroacetate (12.2 g, 0.1 mol), cyclopentanone (8.4 g, 0.1 mol), and dry diglyme (50 ml) were stirred at ice-salt temperatures. Potassium t-butoxide (11.6 g, 0.1 mol) was added over a period of 1.25 hours and the resultant mixture was stirred at that temperature for two hours, then at room temperature for five hours. Hydrochloric acid (6N) was added until the solution was slightly acidic (yellow to pH paper) and solids were removed by centrifugation and filtration and washed with ether. Solvent was removed from the filtrate by evaporation to give a dark oil which on distillation gave 7.84 g (46%) of ethyl β , β -tetramethyleneglycidate: bp 80-84° (2-3 mm) [Lit. 90-95° (3-4 mm)];⁹⁶ ir (liquid film) 3000 (CH) and 1750 cm^{-1} (C = O); nmr (CCl_4) δ 1.29 (t, 3, CH_3), 1.78 [broad m, $(\text{CH}_2)_4$], 3.33 (s, 1, CH), and 4.18 (q, 2, CH_2CH_3). The nmr spectrum also contained signals indicative of some t-butyl β , β -tetramethyleneglycidate as a major impurity.

* This procedure was patterned after a similar synthesis by U. V. Moyer.⁹⁵

3,3-Tetramethylene-4-Hydroxy-5-Pyrazolidone^{28a}

Hydrazine hydrate (0.29 g, 5.9 mmol) was added to ethyl β , β -tetramethyleneglycidate (1.0 g, 5.9 mmol) and the resultant mixture was warmed on a steam bath for 20 minutes. On cooling to room temperature 0.26 g (28%) of 3,3-tetramethylene -4-hydroxy-5-pyrazolidone precipitated. This was recrystallized from ethanol: mp 181-183° (Lit. 184-185°);^{28a} ir (nujol) 1685 cm^{-1} (C = O); nmr (D_2O) δ 2.13 [broad m, 8, (CH_2)₄], and 4.76 (s, 1, CH); molecular weight 155.

Sodium and Lithium 1-t-Butyl-2-Aziridinecarboxylate (53 and 49)

Sodium and lithium 1-t-butyl-2-aziridinecarboxylate (53 and 49) were prepared according to procedures patterned after those of C. L. Moyer.⁴⁰

Methyl 1-t-butyl-2-aziridinecarboxylate (5, 10 g 0.064 mol) and sodium hydroxide (2.04 g, 0.051 mol) were stirred in water (25 ml) at room temperature overnight. The resulting clear solution was then washed twice with chloroform (20 ml) and evaporated to a fine powder. The powder was dried under vacuum to give 8.14 g (96%) of the sodium salt (53) which was identified by spectral properties.

Lithium 1-t-butyl-2-aziridinecarboxylate (49) was prepared in an analogous manner (14.0 g, 94%) from lithium hydroxide monohydrate (4.2 g, 0.1 mol) and 1-t-butyl-2-aziridinecarboxylate (15.7 g, 0.1 mol).

Sodium Cis-1-t-Butyl-3-Methyl-2-Aziridinecarboxylate (67)

Methyl cis-1-t-butyl-3-methyl-2-aziridinecarboxylate (65, 7.35 g, 0.043 mol) was stirred overnight at room temperature with sodium hydroxide (1.68 g, 0.042 mol) in water (50 ml). The resulting solution was washed with chloroform and evaporated to 7.44 g (99%) of the sodium salt (67): ir (nujol) 1600 cm^{-1} (CO_2^-); nmr (D_2O ; spectrum No 3) δ 1.30 (s, 9, t-butyl), 1.44 (d, 3, CH_3), 2.48 (m, 1, C_3H), and 2.74 (d, 1, C_2H).

Sodium Trans-1-t-Butyl-3-Methyl-2-Aziridinecarboxylate (68)

Methyl trans-1-t-butyl-3-methyl-2-aziridinecarboxylate (66, 1.20 g, 7.0 mmol) and sodium hydroxide (0.28 g, 7.0 mmol) were stirred together in water (15 ml) at room temperature overnight. The resulting solution was evaporated to 1.19 g (96%) of the sodium salt (68): ir (nujol) 1615 and 1590 cm^{-1} (CO_2^-); nmr (D_2O ; spectrum No 4) δ 1.45 (s, 9, t-butyl), 1.58 (d, 3, $J = 6\text{ Hz}$, CH_3), and 2.61 (m, 2, ring protons).

Triphenylmethyl 1-t-Butyl-2-Aziridinecarboxylate (91)

Sodium 1-t-butyl-2-aziridinecarboxylate (53, 8.0 g, 0.048 mol) was added to benzene (200 ml), and then some benzene (25 ml) was removed by distillation to remove water. Solid triphenylmethyl bromide (8.0 g, 0.0248 mol) was added along with enough benzene to make the total volume about 200 ml. The resulting slurry was stirred rapidly at a reflux for 14 hours, then cooled to room temperature. Solids were

removed by filtration through filter cell and washed with benzene. The filtrate was evaporated to an oil which was treated with hexanes (15 ml) and placed in a refrigerator to precipitate 5.2 g (52%) of triphenylmethyl 1-t-butyl-2-aziridinecarboxylate (91). Repeated recrystallizations from hexanes gave a pure product: mp 117-118°; ir (nujol) 1730 (C = O), 790 and 710 cm^{-1} (phenyl); nmr (CCl_4 ; spectrum No 10) δ 0.95 (s, 9, t-butyl), 1.59 (dd, 1, ring proton), 1.92 (dd, 1, ring proton), 2.12 (dd, 1, ring proton), and 7.20 (m, 15, triphenylmethyl); molecular weight 385.

Anal. Calcd for $\text{C}_{26}\text{H}_{27}\text{NO}_2$: C, 81.01; H, 7.06; N, 3.63.

Found: C, 81.00; H, 7.16; N, 3.62.

Pyrolysis of Triphenylmethyl 1-t-Butyl-2-Aziridine-
carboxylate (91) in Benzene

Benzene (10 ml) was added to triphenylmethyl 1-t-butyl-2-aziridinecarboxylate (91, 0.40 g, 1.0 mmol) in a thick-walled glass tube (25 cm x 1.5 cm). The tube was flushed with dry nitrogen, cooled in a dry ice-acetone slush, sealed, and placed in an oven (175-180°) for 14 hours. When the tube was again cooled in a dry ice-acetone slush and opened, considerable pressure was released. After concentrating the contents of the tube to an oil, the reaction mixture was column chromatographed (10% alumina, 1.0 cm x 30 cm, 30 g) using cyclohexane as the eluent. Two components were isolated and characterized.

The first component to come off the column was 0.16 g (45%) of 1-t-butyl-2-triphenylmethylaziridine (95). This was recrystallized from ethanol: mp 114-115°; ir (nujol) 1325 and 1430 cm^{-1} (phenyl); nmr (CDCl_3 ; spectrum No 11) δ 0.83 (s, 9, t-butyl), 1.02 (dd, 1, ring

proton), 1.50 (dd, 1, ring proton), 2.90 (dd, 1, ring proton), and 7.2 (broad s, 15, triphenylmethyl); molecular weight 341.

Anal. Calcd for $C_{25}H_{27}N$: C, 87.93; H, 7.97; N, 4.10.

Found: C, 87.98; H, 8.09; N, 4.00.

The second component to come off the column was 0.08 g (25%) of a colorless solid characterized as N-t-butyl-triphenylmethylethylamine (96). This was recrystallized from ethanol: mp 108-109°; ir (KBr) 3040 (NH), 764 and 699 cm^{-1} (phenyl); nmr (CCl_4) δ 0.36 (broad, 1, NH), 1.04 (s, 9, t-butyl), 3.65 (s, 2, CH_2), and 7.19 (s, 15, triphenylmethyl); molecular weight 330.

Anal. Calcd for $C_{24}H_{27}N$: C, 87.49; H, 8.26; N, 4.25.

Found: C, 87.62; H, 8.31; N, 4.30.

Thermal Decomposition of Triphenylmethyl 1-t-Butyl-
2-Aziridinecarboxylate (91) in Cumene

Cumene was purified according to the procedure of U. V. Moyer.⁹⁵ Triphenylmethyl 1-t-butyl-2-aziridinecarboxylate (91, 0.45 g, 1.17 mmol) was dissolved in cumene (8 ml) in a thick walled glass tube fitted with a ground glass joint. The solution was degassed by alternately freezing and thawing the solution under vacuum (0.05 mm). The tube was sealed in vacuo and placed in an oven ($180 \pm 10^\circ$) for 16 hours. The tube was then cooled and opened, and the contents examined.

Gas chromatography (SE-30, 5 ft. x 0.12 in., 238°) showed no trace of dicumyl. By examination of standard solutions it was estimated that 0.2% of the theoretical amount of dicumyl could be detected.

The solution was then evaporated to a crude oil. Nmr observation showed the reaction mixture to be essentially identical to the reaction

in benzene. It was estimated that 1-t-butyl-2-triphenylmethylaziridine (95) comprises 57% of the reaction products and N-t-butyl-triphenyl-methylmethylaniline (96) 32%. By column chromatography 0.23 g (57%) of the aziridine (95) and 0.05 g (12%) of the amine were recovered.

Pyrolysis of Triphenylmethyl 1-t-Butyl-2-Aziridinecarboxy-
late (91) in Benzene in the Presence of t-Butanol

Triphenylmethyl 1-t-butyl-2-aziridinecarboxylate (91, 0.45 g, 1.17 mmol), t-butanol (0.08 g, 1.17 mmol), and benzene (8 ml) were placed in a glass tube. Dry nitrogen was bubbled through the solution, and the tube was sealed after cooling in a dry ice-acetone slush. The tube was then placed in an oven ($160 \pm 10^\circ$) for ten hours, cooled, and opened. The contents of the tube smelled faintly of formaldehyde. The benzene solution was washed with water. The water wash gave a positive color test with Fuchsin-aldehyde reagent.⁹⁷ When treated with aqueous dimedone reagent a colorless solid precipitated which was recrystallized from ethanol-water to give colorless needles: mp $188-189^\circ$ (Lit. formaldehyde-dimedone derivative: 189°).⁹⁸

The benzene layer was dried (MgSO_4) and evaporated to 0.44 g of an oil. The nmr spectrum indicated that the oil consisted of 1-t-butyl-2-triphenylmethylaziridine (95, 11%) and N-t-butyl-triphenyl-methylmethylaniline (96, 88%). The oil was recrystallized from ethanol to give the 0.172 g (50%) of the amine (96): mp $105-107^\circ$.

Thermal Stability of 1-t-Butyl-2-Triphenylmethylaziridine (95)

The aziridine (95, 0.05 g) was dissolved in benzene and placed in a thick-walled glass tube. Nitrogen was bubbled through the solu-

tion, and the tube was cooled in a dry ice-acetone slush and sealed. It was placed in an oven ($180 \pm 10^\circ$) for 14 hours, cooled, and opened. Tlc (cyclohexane/alumina) showed only one spot due to the starting aziridine. The benzene was evaporated leaving a clean oil, and nmr observation of the oil showed only clean starting aziridine. The oil was recrystallized from ethanol to give 0.38 g (76%) of the aziridine (95).

Pyrolysis of Triphenylmethyl 1-t-Butyl-2-Aziridine-carboxylate (91) in Methanol

Nitrogen was bubbled through a solution of triphenylmethyl 1-t-butyl-2-aziridinecarboxylate (92, 0.50 g, 1.3 mmol) in methanol (5 ml) in a glass tube. The tube was sealed (-70°) and placed in an oven ($120 \pm 10^\circ$) for 14 hours. The solution turned brown. On cooling 0.27 g (75%) of methyl triphenylmethyl ether precipitated. It was identified by comparison to an authentic sample.

The filtrate showed no moving spots on tlc (benzene/alumina). An nmr spectrum of the residual oil left after evaporation of the solvent showed no recognizable signals.

Methyl Triphenylmethyl Ether

This was prepared by a procedure patterned after that of Norris and Young.⁹⁹

Triphenylmethyl bromide (3.73 g, 0.01 mol) and sodium methoxide (0.54 g, 0.01 mol) were refluxed in methanol for ten hours. On cooling 2.26 g (82%) of methyl triphenylmethyl ether precipitated. This was recrystallized from methanol: mp $80-80.5^\circ$ (Lit. $82.6-82.9^\circ$).⁹⁹

Reaction of Lithium 1-t-Butyl-2-Aziridinecarboxylate (49)
with Thionyl Chloride

A sodium hydride suspension (0.96 g, 20.0 mmol), washed three times with cyclohexane, was added to tetrahydrofuran (25 ml) under nitrogen to form a slurry. Lithium 1-t-butyl-2-aziridinecarboxylate (49, 1.0 g, 6.7 mmol) was added to the slurry followed by dropwise addition of thionyl chloride (1.19 g, 10.0 mmol). The resulting mixture was stirred at room temperature for 1.25 hours. Solvent was removed by evaporation, and cyclohexane (35 ml) was added followed by careful addition of water to destroy the sodium hydride present. The organic layer was separated and washed with water, dried (MgSO_4), and, after evaporation of the solvent, distilled to give 0.25 g (23%) of 1-t-butyl-3-chloro-2-azetidinone (50): bp 70° (0.2 mm); ir (liquid film) 1760 ($\text{C}=\text{O}$), 814, 745, and 695 cm^{-1} ($\text{C}-\text{Cl}$); nmr (CCl_4 ; spectrum No 12) δ 1.31 (s, 9, t-butyl), 3.18 (dd, 1, CH), 3.78 (dd, 1, CH), and 4.57 (dd, 1, CH); molecular weight 161, 163.

Anal. Calcd for $\text{C}_{17}\text{H}_{12}\text{NOCl}$: C, 52.01; H, 7.43; N, 8.67.

Found: C, 52.27; H, 7.65; N, 8.46.

Slightly improved yields could be obtained by removing excess sodium hydride and salts by filtration followed by distillation of the residual oil: 33%.

Reaction of Sodium 1-t-Butyl-2-Aziridinecarboxylate (53)
with Oxalyl Chloride*

Solid sodium 1-t-butyl-2-aziridinecarboxylate (53), 1.05 g, 6.3 mmol) was added to a solution of oxalyl chloride (0.95 g, 7.5 mmol) in benzene (10 ml) at room temperature. Both heat and gas were evolved. The resulting slurry was refluxed for 15 minutes. Benzene (20 ml) was added, and the slurry was washed with aqueous sodium carbonate, water, and dried (MgSO_4). Distillation of the residual oil left after evaporation of the solvent gave 0.266 g (26%) of 1-t-butyl-3-chloro-2-azetidinone (50). This was identified by spectral comparison to an authentic sample: bp 90° (0.7 mm).

Reaction of Sodium 1-t-Butyl-2-Aziridinecarboxylate (53)
with Oxalyl Chloride in the Presence of Triethylamine

The sodium salt (53, 1.05 g, 6.3 mmol) was slowly added to a mixture of oxalyl chloride (0.95 g, 7.5 mmol) and triethylamine (0.76 g, 7.5 mmol) in benzene (50 ml). The dark brown slurry was stirred at room temperature for one hour, washed with 5% HCl, sodium carbonate, and water, dried (MgSO_4), and evaporated to 0.30 g (29%) of 1-t-butyl-3-chloro-2-azetidinone (50). This was identified by comparison to an authentic sample.

Reaction of Sodium Cis-1-t-Butyl-3-Methyl-2-Aziridinecarboxylate
(67) with Oxalyl Chloride

The sodium salt (67, 3.4 g, 0.019 mol) was added slowly to a

* This reaction was patterned after a general synthesis of acid chlorides.¹⁰⁰

solution of oxalyl chloride (3.0 g, 0.0238 mol) in benzene (20 ml). The resulting slurry was stirred at ambient temperature for one hour, and then a few chips of ice were added. Benzene (20 ml) was added, and the reaction mixture was washed with sodium carbonate and water, dried (MgSO_4), and evaporated to 3.2 g (98%) of a clean oil which was distilled to give 2.6 g (79%) of cis-1-t-butyl-3-chloro-4-methyl-2-azetidinone (69): bp 65° (0.1 mm); ir (liquid film) 2930 (CH), 1750 cm^{-1} (C = O); nmr (CCl_4 ; spectrum No 15) δ 1.35 (s, 9, t-butyl), 1.40 (d, 3, J = 6.4 Hz, CH_3), 4.01 (m, 1, CHN), and 4.70 (d, 1, J = 5.1 Hz, CHCO); molecular weight 175, 177.

The oil was redistilled for an analytical sample, but even when stored under a vacuum it was unstable at room temperature. Thus it is not surprising that the analytical sample did not check.

Anal. Calcd for $\text{C}_8\text{H}_{14}\text{NOCl}$: C, 54.66; H, 8.03; N, 7.98.

Found: C, 53.83; H, 7.93; N, 8.02.

Reaction of Sodium trans-1-t-Butyl-3-Methyl-2-Aziridinecarboxylate (68) with Oxalyl Chloride

A mixture composed of sodium trans-1-t-butyl-3-methyl-2-aziridinecarboxylate (68, 1.3 g, 3.0 mmol) and an inert salt was added slowly to a solution of oxalyl chloride (1.09 g, 8.7 mmol) in benzene (25 ml). The resulting slurry was stirred at room temperature for one hour, washed with 5% HCl, aqueous sodium carbonate, and water, and dried (MgSO_4). The solution was evaporated to 0.33 g (63%) of trans-1-t-butyl-3-chloro-4-methyl-2-azetidinone (70). The oil was distilled for an analytical sample: bp 65° (0.1 mm); ir (liquid film) 2900 (CH) and 1751 cm^{-1} (C = O); nmr (CCl_4 ; spectrum No 18) δ 1.34 (s, 9, t-butyl),

1.45 (d, 3, $J = 6.1$ Hz, CH_3), 3.68 (m, 1, CHN), and 4.09 (d, 1, $J = 1.7$ Hz, CHCO); molecular weight 175, 177.

Anal. Calcd for $\text{C}_8\text{H}_{14}\text{NOC}$: C, 54.66; H, 8.03; N, 7.98.

Found: C, 54.79; H, 7.91; N, 7.87.

Ring Expansion of Sodium 1-t-Butyl-2-Aziridinecarboxylate (53)
with Nosyl Chloride in Acetonitrile

The sodium salt (53, 0.77 g, 4.7 mmol) and nosyl chloride (1.02 g, 4.7 mmol) were stirred together in benzene (50 ml) for four hours at room temperature. The slurry was washed with water, dried (MgSO_4), and evaporated to an oil which consisted of a mixture of nosyl chloride and 1-t-butyl-2-aziridinecarboxylic acid anhydride (73a; spectrum No 20). The oil was taken up in a solution of tetraethyl ammonium chloride (2.68 g, 16.0 mmol) in acetonitrile and left at room temperature overnight. The resulting orange solution was evaporated to an oil, taken up in petroleum ether (bp 37-46°), washed with water, dried (MgSO_4), and evaporated to a pale yellow oil (0.202 g) which was shown by nmr spectroscopy to consist of 1.3 g (17%) of 1-t-butyl-3-chloro-2-azetidinone (50) together with some extraneous material.

Ring Expansion of Sodium Cis-1-t-Butyl-3-Methyl-2-Aziridine-
carboxylate (67) with Nosyl Chloride in Acetonitrile

The sodium salt (67, 0.37 g, 2.0 mmol) and nosyl chloride (0.44 g, 2.0 mmol) were stirred together in benzene (50 ml) for four hours at room temperature. The slurry was washed with water, dried (MgSO_4), and evaporated to an oil. The oil was dissolved in a solution of tetraethyl ammonium chloride (0.33 g, 2.0 mmol) and left at room temperature

overnight. Acetonitrile was removed by evaporation and the residual oil was taken up in petroleum ether (bp 37-46°), washed with water, dried (MgSO_4), and evaporated to 0.274 g (75%) of an oil identified as cis-1-t-butyl-3-chloro-4-methyl-2-azetidinone (69). Distillation (65°, 0.1 mm) gave 0.17 g (50%) of the pure product.

Reaction of Sodium Cis-1-t-Butyl-3-Methyl-2-Aziridinecarboxylate (67)
with Nosyl Chloride

The sodium salt (67, 0.5 g, 2.9 mmol) and nosyl chloride (0.64 g, 2.9 mmol) were stirred at room temperature in benzene (50 ml) for 4.5 hours. The resulting slurry was washed with aqueous sodium carbonate and water, dried (MgSO_4), and evaporated to an oil consisting of a mixture of cis-1-t-butyl-3-methyl-2-aziridinecarboxylic anhydride (73b) and nosyl chloride. Nosyl chloride (0.13 g) was removed by several crystallizations from petroleum ether. The anhydride (73b) was obtained free of nosyl species by evaporation of the solvent from the mother liquor to give 0.24 g (56%) as an oil.

Cis-1-t-Butyl-3-Methyl-2-Aziridinecarboxylic Anhydride (75)

Sodium cis-1-t-butyl-3-methyl-2-aziridinecarboxylate (67), 1.0 g, 5.8 mmol) and nosyl chloride (0.62 g, 2.8 mmol) were stirred together in benzene at room temperature for 4.5 hours. The resulting slurry was washed with water, aqueous sodium carbonate, and again with water, dried (MgSO_4), and evaporated to 0.633 g (76%) of an oil identified as cis-1-t-butyl-3-methyl-2-aziridinecarboxylic anhydride (73b). The oil was taken up in petroleum ether (bp 37-46°) and filtered to remove a fine insoluble suspension. Evaporation of the filtrate gave 0.574 g

(69%) of the anhydride (73b) as an oily solid: ir (liquid film) 2920 (CH), 1820, 1800, and 1760 cm^{-1} ($\text{C}=\text{O}$); nmr (CCl_4 ; spectrum No 21) δ 1.0 (s, 9, t-butyl), 1.26 (broad d, 3, CH_3), and 2.15 (m, 2, ring protons).

Reaction of Cis-1-t-Butyl-3-Methyl-2-Aziridinecarboxylic Anhydride (75) with Sodium Methoxide in Methanol in the Presence of Nosyl Chloride

Sodium cis-1-t-butyl-3-methyl-2-aziridinecarboxylate (67, 0.34 g, 2.0 mmol) and nosyl chloride (0.44 g, 2.0 mmol) were stirred at room temperature in benzene, washed with water, dried (MgSO_4), and evaporated to an oil composed of the anhydride (75) and nosyl chloride. The oil was dissolved in a solution of sodium methoxide (0.10 g, 1.8 mmol) in methanol and left at room temperature overnight. The resulting solution was poured into benzene and washed with water. The benzene layer was dried (MgSO_4) and evaporated to an oily solid. The residue was taken up in chloroform and the solids were removed by filtration. The chloroform solution was evaporated to 0.118 g (35%) of an oil identified as methyl cis-1-t-butyl-3-methyl-2-aziridinecarboxylate (65) by spectroscopy.

The water layer was evaporated to a solid which was identified as a mixture of sodium nosylate and sodium cis-1-t-butyl-3-methyl-2-aziridinecarboxylate (67) by nmr spectroscopy.

Reaction of Sodium Trans-1-t-Butyl-3-Methyl-2-Aziridinecarboxylate (68) with Nosyl Chloride

Sodium trans-1-t-butyl-3-methyl-2-aziridinecarboxylate (68, 0.3 g, 1.7 mmol) and nosyl chloride (0.388 g, 1.7 mmol) were stirred in benzene

at room temperature for four hours. The resulting slurry was washed with aqueous sodium carbonate and water, dried (MgSO_4), and evaporated to an oil (0.38 g) consisting of a mixture of trans-1-t-butyl-3-methyl-2-aziridinecarboxylic anhydride (73c) and unreacted nosyl chloride: nmr (CCl_4 ; spectrum No 20) δ 1.17 (s, 9, t-butyl), 1.42 (m, 3, CH_3), 2.30 (d, 1, C_2H), and 2.60 (m, 1, C_3H).

Nmr of the Anhydrides in Sulfur Dioxide

The anhydrides were dissolved in liquid sulfur dioxide at -10° and transferred in a laboratory atmosphere to nmr sample tubes which were sealed. Samples of the anhydrides with nosyl or tosyl chloride present were prepared by treating the appropriate sodium salts with equimolar amounts of the arylsulfonyl chlorides and dissolving the residual oil left after the usual workup in sulfur dioxide as above. The same spectra could be obtained by adding the arylsulfonyl chlorides to solutions of the anhydride in sulfur dioxide, but this was found to be less convenient.

The chemical shifts for the ionized and unionized anhydrides are reported with reference to external tetramethylsilane in carbon tetrachloride and are tabulated in Tables IV and V.

The solution of the cis anhydride in the presence of nosyl chloride or tosyl chloride (after ionization had occurred) was quenched by pouring the sulfur dioxide solution into a solution of tetraethyl ammonium chloride in acetonitrile. After the usual workup cis-1-t-butyl-3-chloro-4-methyl-2-azetidinone was recovered in yields of 13% and 14% respectively.

Nmr Spectra of 3-Chloro-2-Azetidinones in Antimony
Pentafluoride-Sulfur Dioxide

Sulfur dioxide (2 ml) at -10° was saturated with antimony pentafluoride and cooled to -70° . Approximately 300 mg of 1-t-butyl-3-chloro-2-azetidinone (50) was dissolved in the resultant solution, and an aliquot was sealed in an nmr sample tube. The spectrum of the solution (spectrum No 14) was compared to a spectrum of the same azetidinone in sulfur dioxide (spectrum No 13), and both are reported in Table VI. The antimony pentafluoride-sulfur dioxide solution was poured into a solution of sodium methoxide in methanol (-70°). This solution was then warmed to room temperature, poured into water, and extracted with benzene. The benzene layer was dried (MgSO_4), and evaporated to a colorless oil identified as extremely clean 1-t-butyl-3-chloro-2-azetidinone (50).

In a similar fashion cis-1-t-butyl-3-chloro-4-methyl-2-azetidinone (69) was treated with antimony pentafluoride in sulfur dioxide. The nmr spectra are recorded as above, and workup of the solution with sodium methoxide in methanol yielded only extremely clean cis-1-t-butyl-3-chloro-4-methyl-2-azetidinone (69).

Reduction of 1-t-Butyl-3-Chloro-2-Azetidinone (50) with Zinc

Zinc dust (2.5 g, 30 mmol), activated by stirring two minutes in concentrated hydrochloric acid, washing 4 times with distilled water and 4 times with acetone (reagent grade), and drying in vacuo for 15 minutes,¹⁰¹ was added to a solution of 1-t-butyl-3-chloro-2-azetidinone (50, 0.40 g, 2.49 mmol) in ethanol. The heterogeneous mixture was then refluxed

for ten days, cooled, filtered, and evaporated to an oil. The oil was distilled to give 0.13 g (41%) of 1-t-butyl-2-azetidinone (51): bp 90-100° (25 mm).

1-t-Butyl-2-Azetidinone (51)

This was prepared by a procedure similar to that of Blicke and Gould.³⁹

Triethylamine (3.55 g, 35.0 mmol) was added in dry tetrahydrofuran (10 ml). A solution of thionyl chloride (1.4 g, 12.0 mmol) in tetrahydrofuran (10 ml) was slowly added to the stirred slurry. The resulting yellow mixture was stirred at room temperature for 14 hours, then filtered through filter cell, and the filtrate was evaporated to a dark brown sludge. The sludge was washed through 5% alumina with chloroform, and the eluent was evaporated to 0.085 g (7%) of a yellow oil identical to the 1-t-butyl-2-azetidinone prepared by reduction of 1-t-butyl-3-chloro-2-azetidinone (50): ir (liquid film) 2900 (CH) and 1740 cm^{-1} (C = O); nmr (CCl_4 ; spectrum No 19) δ 1.28 (s, 9, t-butyl), 2.68 (m, 2, CH_2), and 3.12 (m, 2, CH_2); molecular weight 127.

Anal. Calcd for $\text{C}_7\text{H}_{13}\text{NO}$: C, 66.11; H, 10.30; N, 11.01.

Found: C, 66.02; H, 10.46; N, 10.92.

Reaction of 1-t-Butyl-3-Chloro-2-Azetidinone (50)
with Sodium Hydroxide

1-t-Butyl-3-chloro-2-azetidinone (50, 0.20 g, 1.2 mmol) was stirred with a solution of sodium hydroxide (0.06 g, 1.5 mmol) in water (5 ml) for two hours. The mixture was then refluxed for three hours. The

resulting solution was cooled, and solvent was removed by evaporation to give 0.245 g (94%) of a pale yellow powder in which the sole organic species present was identified as sodium 1-t-butyl-2-aziridinecarboxylate (53) by comparison of the ir and nmr spectra with spectra of an authentic sample.

Reaction of 1-t-Butyl-3-Chloro-2-Azetidinone (50)
with Sodium Methoxide

In a dry box 1-t-butyl-3-chloro-2-azetidinone (50, 0.31 g, 1.8 mmol) was added to a solution of sodium methoxide (0.16 g, 3.0 mmol) in methanol (2.5 ml) and left at room temperature for two days. The reaction mixture was poured into benzene (15 ml), washed with water, dried (MgSO_4), and evaporated to 0.14 g (48%) of an oil identified as methyl 1-t-butyl-2-aziridinecarboxylate (5) by comparison of ir and nmr spectra with the spectra of an authentic sample.

Reaction of Cis-1-t-Butyl-3-Chloro-4-Methyl-2-Azetidinone (69)
with Sodium Hydroxide

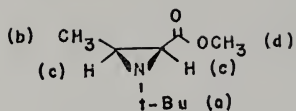
The azetidinone (69, 0.30 g, 1.7 mmol) was dissolved in dioxane (1 ml), and the resulting solution was added to a solution of sodium hydroxide (0.16 g, 40.0 mmol) in water (2 ml). More water was added until the mixture became clear, and the solution was left at room temperature for 30 days. It was then washed with ether and evaporated to 0.38 g (83%) of a white powder identified as sodium cis-1-t-butyl-3-methyl-2-aziridinecarboxylate (67) by comparison of the ir and nmr spectra with the spectra of a known sample.

Reaction of Trans-1-t-Butyl-3-Chloro-4-Methyl-2-Azetidinone (70)
with Sodium Hydroxide

The azetidinone (70, 0.30 g, 1.7 mmol) was dissolved in dioxane (1 ml), and the resulting solution was added to a solution of sodium hydroxide (0.18 g, 45.0 mmol) in water (2 ml). Water was added until the mixture became clear, and the resulting solution was left at room temperature for 21 days. It was washed with chloroform and evaporated to a white solid. Nmr observation showed that about 30% of the solid consisted of sodium trans-1-t-butyl-3-methyl-2-aziridinecarboxylate (68). The other components of the mixture were not characterized.

SPECTRA

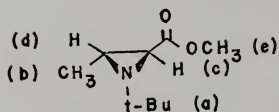
No 1



SOLVENT CCL₄

- a. 0.95
- b. 1.17
- c. 2.05
- d. 3.65

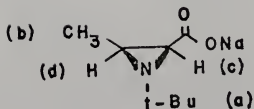
No 2



SOLVENT CCL₄

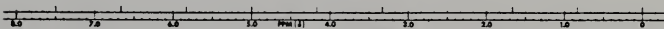
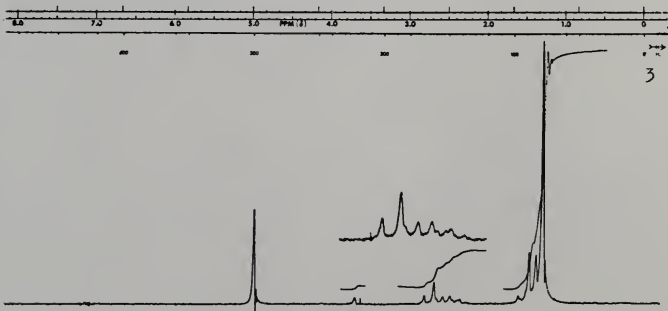
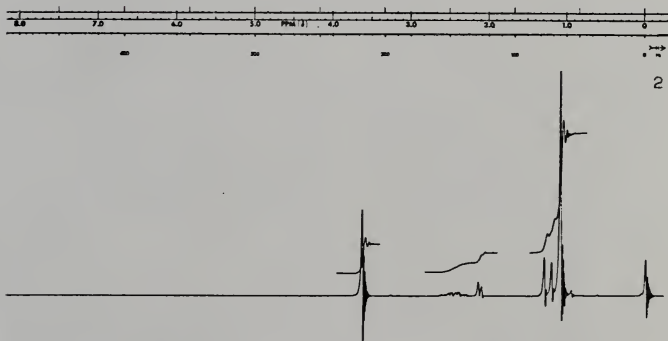
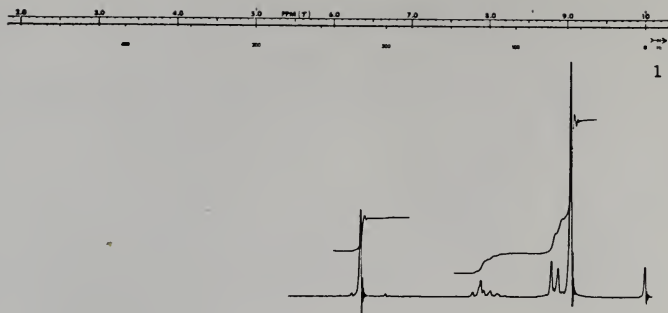
- a. 1.10
- b. 1.26
- c. 2.13
- d. 2.46
- e. 3.63

No 3

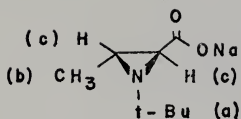


SOLVENT D₂O

- a. 1.30
- b. 1.44
- c. 2.48 or 2.74
- d. 2.48 or 2.74



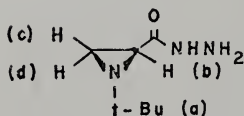
No 4



SOLVENT D₂O

- a. 1.45
- b. 1.58
- c. 2.61

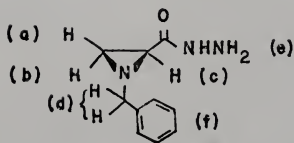
No 5



SOLVENT D₂O

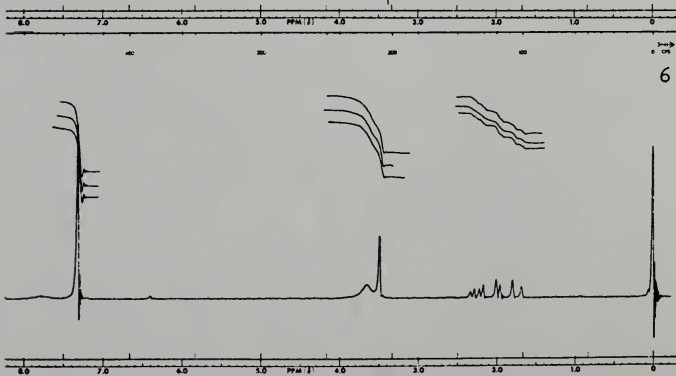
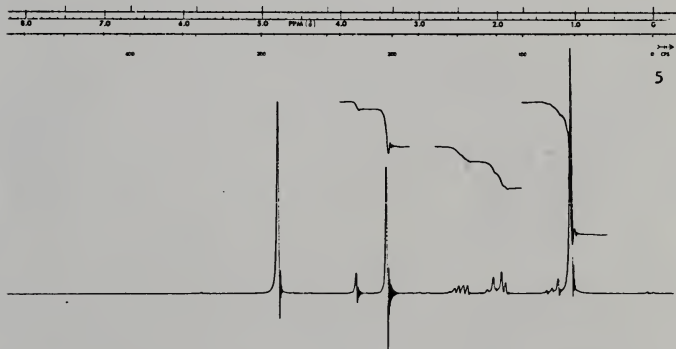
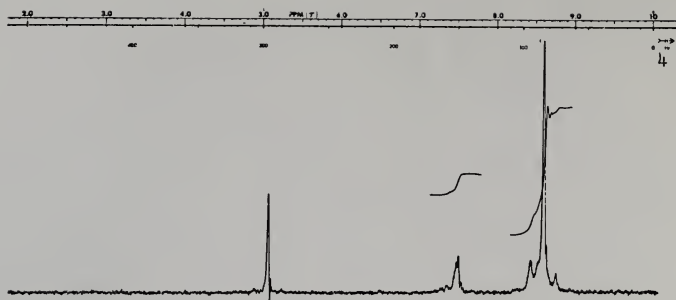
- a. 1.26
- b. 2.64 or 2.17
- c. 2.64 or 2.17
- d. 2.64 or 2.17

No 6

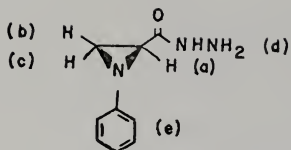


SOLVENT CDCl₃

- a. 1.79 or 2.25
- b. 1.79 or 2.25
- c. 1.79 or 2.25
- d. 3.5
- e. 3.65
- f. 7.31



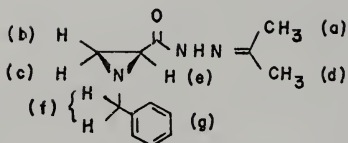
No 7



SOLVENT CDCl_3

- a. 2.32 or 2.78
- b. 2.32 or 2.78
- c. 2.32 or 2.78
- d. 4.05
- e. 7.05

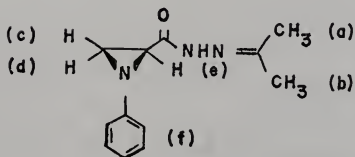
No 8



SOLVENT CDCl_3

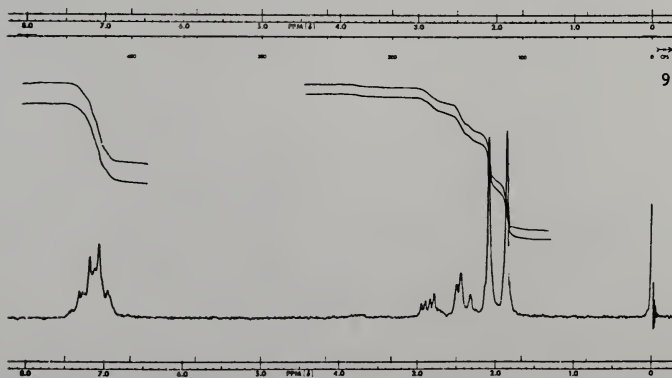
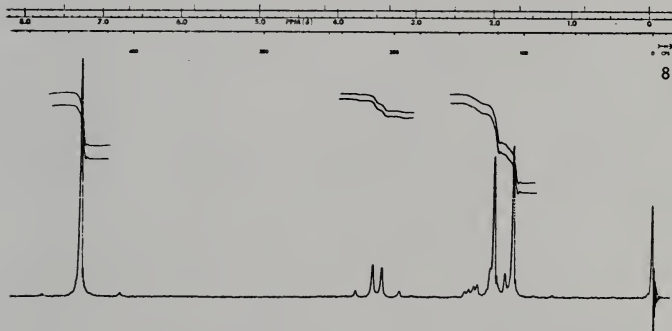
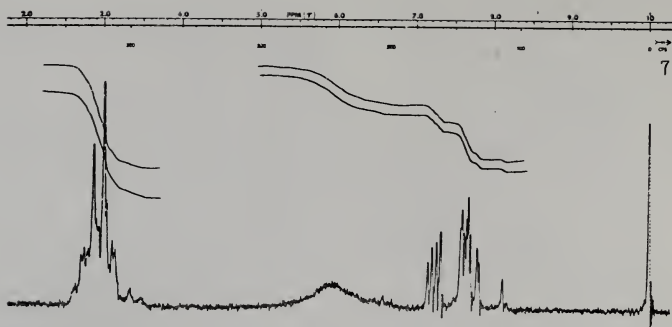
- a. 1.79 or 2.04
- b. 1.95 or 2.35
- c. 1.95 or 2.35
- d. 1.79 or 2.04
- e. 1.95 or 2.35
- f. 4.55
- g. 7.31

No 9

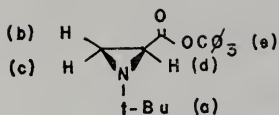


SOLVENT CDCl_3

- a. 1.85 or 2.09
- b. 1.85 or 2.09
- c. 2.31 or 2.87
- d. 2.31 or 2.87
- e. 2.31 or 2.87
- f. 7.1



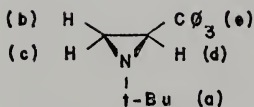
No 10



SOLVENT CDCl₃

- a. 0.95
- b. 1.59, or 1.92, or 2.12
- c. 1.59, or 1.92, or 2.12
- d. 1.59, or 1.92, or 2.12
- e. 7.26

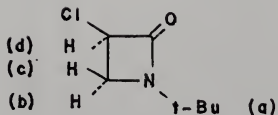
No 11



SOLVENT CDCl₃

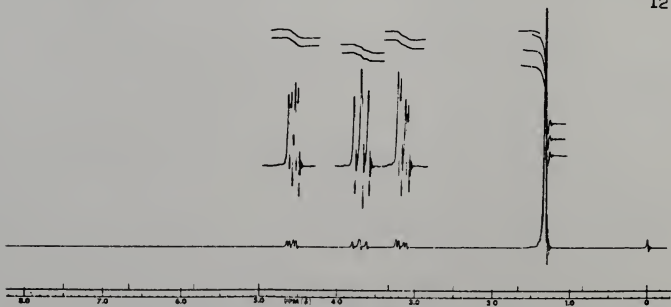
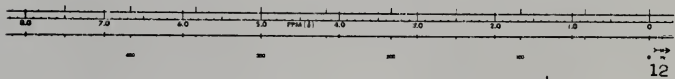
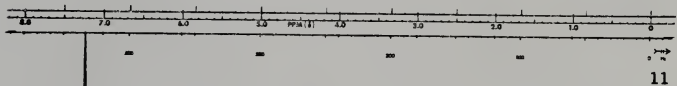
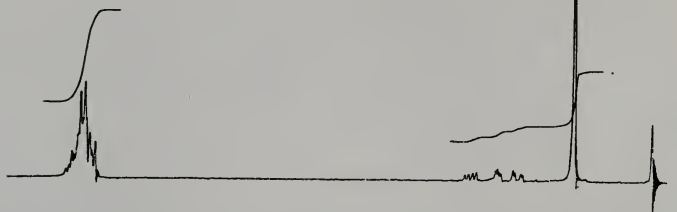
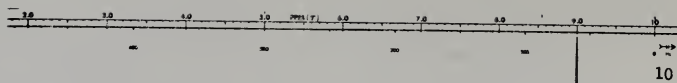
- a. 0.83
- b. 1.02, or 1.50, or 2.90
- c. 1.02, or 1.50, or 2.90
- d. 1.02, or 1.50, or 2.90
- e. 7.2

No 12

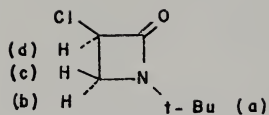


SOLVENT CCl₄

- a. 1.31
- b. 3.18
- c. 3.78
- d. 4.57



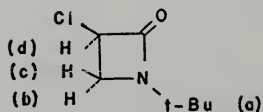
No 13



SOLVENT SO_2

- a. 0.75
- b. 2.70
- c. 3.18
- d. 4.08

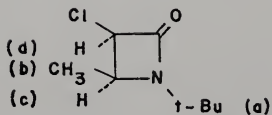
No 14



SOLVENT $\text{SbF}_5 \cdot \text{SO}_2$

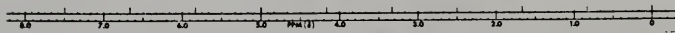
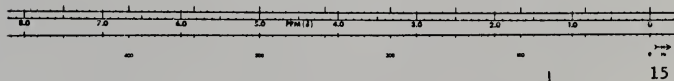
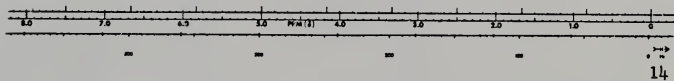
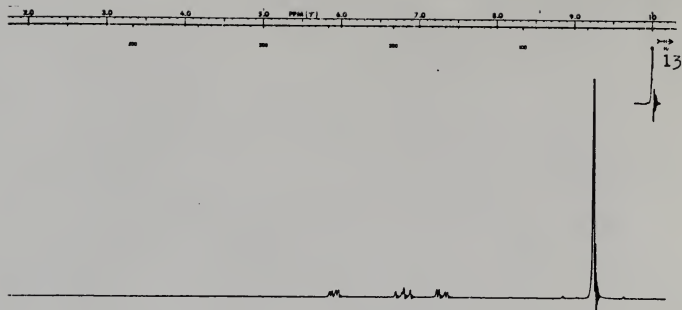
- a. 1.15
- b. 3.59
- c. 4.02
- d. 4.89

No 15

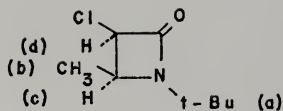


SOLVENT CCl_4

- a. 1.35
- b. 1.40
- c. 4.01
- d. 4.70



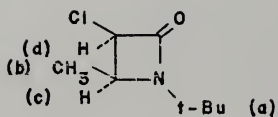
No 16



SOLVENT SO₂

- a. 0.76
- b. 0.80
- c. 3.56
- d. 4.22

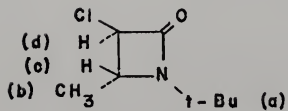
No 17



SOLVENT SbF₅·SO₂

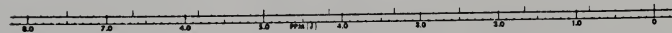
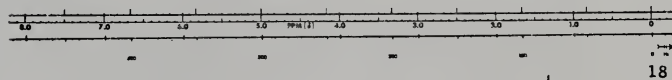
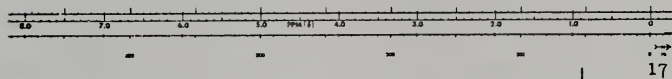
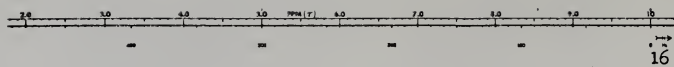
- a. 1.08
- b. 1.25
- c. 4.37
- d. 4.95

No 18



SOLVENT CCl₄

- a. 1.34
- b. 1.45
- c. 3.68
- d. 4.09



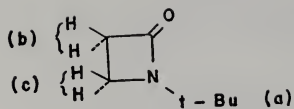
No 19

SOLVENT CCl_4

a. 1.28

b. 2.68

c. 3.12



No 20

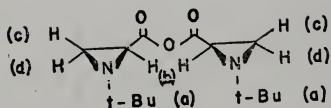
SOLVENT CCl_4

a. 1.0

b. 1.88 or 2.25

c. 1.88 or 2.25

d. 1.88 or 2.25



No 21

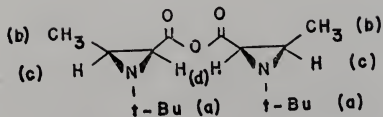
SOLVENT CCl_4

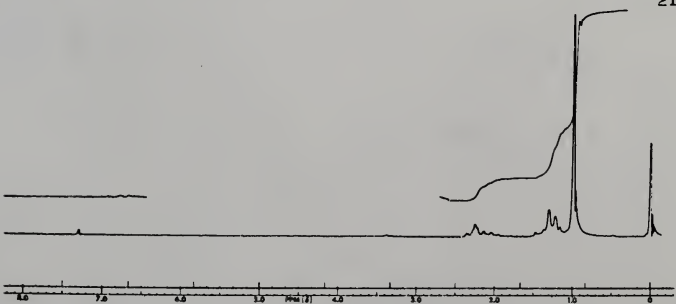
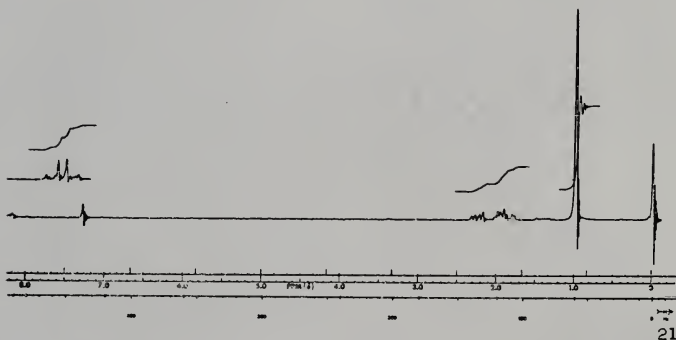
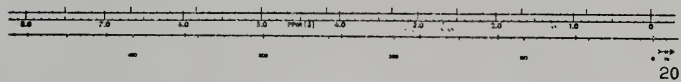
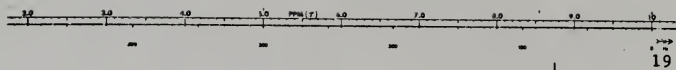
a. 1.0

b. 1.26

c. 2.15

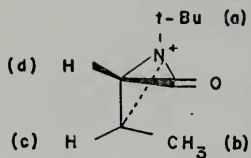
d. 2.15





No 22

SOLVENT SO_2



a. 0.78

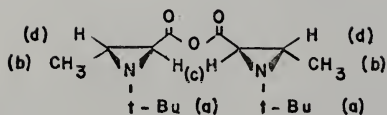
b. 0.95

c. 2.80

d. 2.80

No 23

SOLVENT CCl_4



a. 1.17

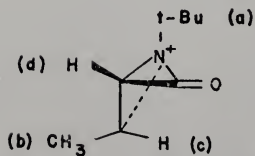
b. 1.42

c. 2.30

d. 2.60

No 24

SOLVENT SO_2

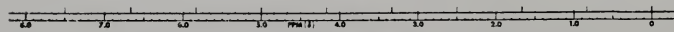
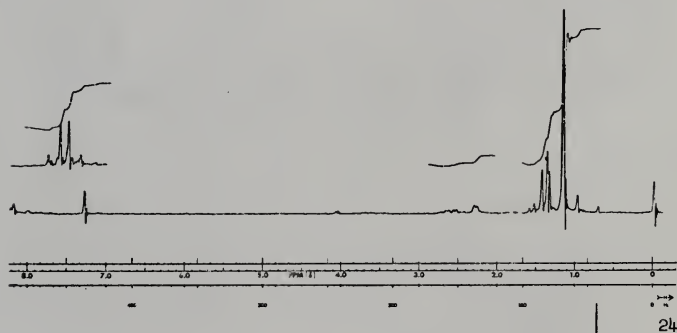
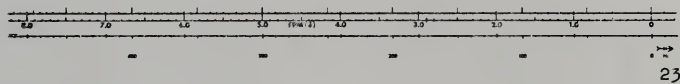
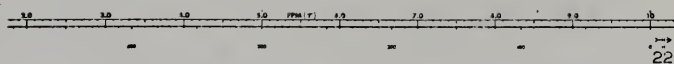


a. 0.88

b. 1.15

c. 2.80

d. 2.80



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BIOGRAPHICAL SKETCH

Stuart Chandler Clough was born July 29, 1943, in Richmond, Virginia. In June, 1961, he graduated from Douglas Southall Freeman High School. In June, 1965, he received the degree of Bachelor of Science with a major in chemistry from the University of Richmond. In September, 1965, he enrolled in the Graduate School of the University of Florida where he studied as a NASA Trainee (1965-1968). He then obtained a Graduate School Assistantship (1968-1969), followed by a research assistantship (1969-present) while he continued his study toward the degree of Doctor of Philosophy.

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This dissertation was prepared under the direction of the chairman of the candidate's supervisory committee and has been approved by all members of that committee. It was submitted to the Dean of the College of Arts and Sciences and to the Graduate Council, and was approved as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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